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[Continued on next page]

(54) **Title:** Novel Compositions Useful for Killing DNA Repair-Deficient Cancer Cells, and Methods Using Same

(57) **Abstract:** The invention includes a method of preventing or treating a DNA repair protein-deficient cancer in a subject in need thereof. In certain embodiments, the protein comprises BRCA2. In other embodiments, the protein comprises PTEN.

Fig. 1A

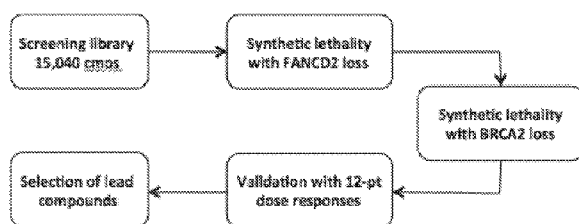


Fig. 1B

	FANCD2 +/+	FANCD2 -/-	BRCA2 +/+	BRCA2 -/-
YU126919	inactive	16.21	8.94	5.56
YU127190	inactive	inactive	12.42	7.92
YU128355	13.3	4.53	1.93	0.84
YU128440	9.59	4.68	2.51	0.97



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— *of inventorship (Rule 4.17(iv))*

Published:

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

— *with sequence listing part of description (Rule 5.2(a))*

TITLE OF THE INVENTION

Novel Compositions Useful for Killing DNA Repair-Deficient Cancer Cells, and
Methods Using Same

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CROSS REFERENCE TO RELATED APPLICATIONS

The present application claims priority under 35 U.S.C. § 119(e) to U.S.
Provisional Patent Application No. 62/101,123, filed January 8, 2015, which is incorporated
herein by reference in its entirety.

10

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR
DEVELOPMENT

This invention was made with government support under CA129186 and
CA168733 awarded by National Institutes of Health. The government has certain rights in
the invention.

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BACKGROUND OF THE INVENTION

In cancer therapy, gene expression profiling and mutational analyses can be
used to inform the optimal choice of treatment and overall prognosis. Personalized cancer
therapies are rapidly becoming the standard of care in clinical practice. Thus, novel drugs
targeting molecular pathways known to be dysregulated in cancer may have utility as first-
line treatments or when treatment has failed.

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Frequently, the inability to properly coordinate repair of damaged DNA
underlies tumorigenesis and disease progression in malignancies. Human cancer syndromes
have been linked to mutations in nearly every DNA repair pathway. These pathways often
exhibit redundancy, and inhibition of additional repair factors may induce synthetic lethality
in repair-deficient tumors while sparing healthy tissue. DNA double-strand break (DSB)
repair pathways are particularly vulnerable, as shown by recent observations that inactivation
of the RAD52 recombinase is lethal in the context of BRCA1, BRCA2 and/or PALB2 loss.

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Synthetic lethality is not limited to defects in a single DNA repair pathway
and may also occur across complementary repair pathways. This is perhaps best
characterized in the relationship between the homology-dependent repair (HDR) and base
excision repair (BER) pathways. Incompletely resolved lesions that are substrates of BER
(*e.g.*, alkylated and damaged bases) generate DNA single-strand breaks (SSBs) that persist

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into S-phase, leading to stalling and collapse of DNA replication forks and induction of DSBs that must be resolved by HDR. This is exemplified by the enhanced toxicity of poly (ADP-ribose) polymerase (PARP) inhibitors in BRCA1- and BRCA2-deficient cells. Notably, olaparib, a PARP inhibitor, has shown potential in the treatment of BRCA-mutant ovarian malignancies, which are often metastatic at time of diagnosis, limiting therapeutic options.

Genetic instability is a hallmark of cancer and can quickly confer resistance to even targeted monotherapies or drug combinations. Inhibition of DNA repair pathways can decrease resistance by altering the response of tumor cells to DNA-damaging chemotherapy and ionizing radiation (IR). Inhibition of the BER pathway in a BRCA2-mutant background sensitizes cells to the DNA methylating agent temozolomide. Conversely, even in an HDR-defective background, intact DNA mismatch repair is necessary for certain DNA lesions to induce cytotoxicity, rendering mismatch repair-defective cells highly resistant to alkylation and crosslinking. Efforts to identify effective radiosensitizing agents have also met with recent success and continue to represent an area of high translational potential. Given that improving genomic techniques will soon enable profiling of entire gene pathways in tumors, it is likely that selection of cancer therapies will increasingly be guided by elucidation of the functional status of DNA repair pathways.

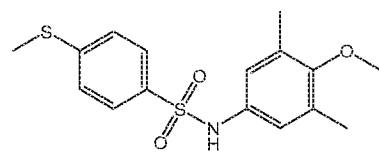
There is a need in the art to identify novel compositions that are useful in killing cancer cells, such as those DNA repair-deficient cancer cells. The present invention addresses and meets this need.

BRIEF SUMMARY OF THE INVENTION

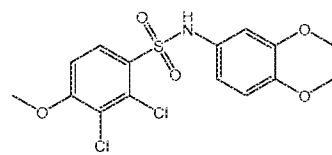
The invention provides a method of treating or preventing a DNA repair protein-deficient cancer in a subject in need thereof.

In certain embodiments, the method comprises administering to the subject a therapeutically effective amount of at least one compound, or a salt or solvate thereof, selected from the group consisting of:

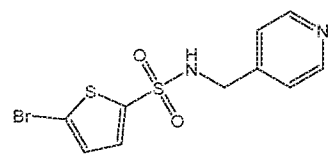
N-(4-methoxy-3,5-dimethyl phenyl)-4-(methylthio)benzenesulfonamide (YU126919)



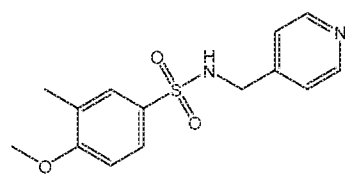
2,3-dichloro-N-(3,4-dimethoxy phenyl)-4-methoxybenzenesulfonamide (YU127190)



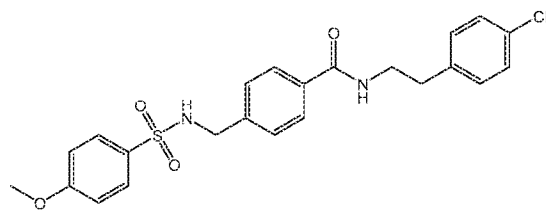
5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide (YU128355)



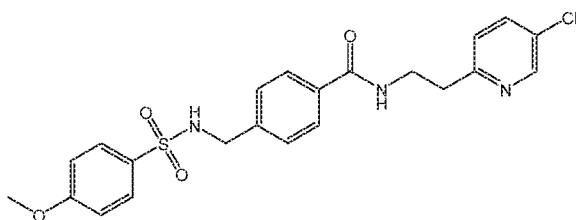
4-methoxy-3-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (YU128440)



N-(4-chlorophenethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide (YU175534)



and, N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide (YU238259)



whereby the cancer is treated or prevented in the subject.

In certain embodiments, the at least one compound inhibits DNA double strand break repair in the cancer. In other embodiments, the at least one compound inhibits homology-dependent DNA repair in the cancer.

In certain embodiments, the cancer is deficient in at least one protein selected from the group consisting of BRCA1, BRCA2, PTEN, ATM, PALB2, FANCD2, CHK2, RAD51 paralogs, MRE11, NBS1, RAD50, ATR, ATRIP, MEN1 and any other Fanconi pathway factors. In other embodiments, the cancer is deficient in at least one selected from the group consisting of BRCA2 and PTEN.

In certain embodiments, the subject is further administered at least one additional antitumor agent. In other embodiments, the antitumor agent is at least one selected from the group consisting of topoisomerase inhibitors; alkylating agents; nitrosoureas; antimetabolites; antitumor antibiotics; antimicrotubule agents; hormonal agents; DNA strand break inducing agents; EGF receptor inhibitors and anti-EGF receptor antibodies; AKT inhibitors; mTOR inhibitors; CDK inhibitors; receptor tyrosine kinase (RTK) inhibitors; ribonucleotide reductase inhibitors; immune checkpoint inhibitors; and miscellaneous agents. In yet other embodiments, administration of the at least one compound and at least one additional antitumor agent is synergistic. In yet other embodiments, the at least one compound and at least one additional antitumor agent are co-administered to the subject. In yet other embodiments, the at least one compound and at least one additional antitumor agent are coformulated. In yet other embodiments, the subject is further administered radiation therapy. In yet other embodiments, administration of the at least one compound and the radiation therapy is synergistic.

In certain embodiments, the at least one compound is administered to the subject through a route selected from the group consisting of oral, transdermal, transmucosal, intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, pleural, peritoneal, subcutaneous, epidural, otic, intraocular, and topical.

In certain embodiments, the cancer comprises at least one selected from the group consisting of breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, glioma, meningioma, glioblastoma multiforme, melanoma, lymphoma, leukemia, lung cancer, endometrial cancer, head and neck cancer, sarcoma, multiple myeloma and neuroblastoma.

In certain embodiments, the cancer comprises at least one selected from the group consisting of breast cancer, ovarian cancer, melanoma, head and neck cancer, sarcoma, multiple myeloma and brain cancer.

In certain embodiments, the cancer is deficient in PTEN activity and wherein the subject is further administered a therapeutically effective amount of an AKT inhibitor.

In certain embodiments, the cancer comprises glioma or melanoma.

In certain embodiments, the subject is a mammal. In other embodiments, the mammal is a human.

The invention further provides a kit comprising at least one compound or a salt or solvate thereof, an applicator, and an instructional material for use thereof. In certain

embodiments, the instructional material comprises instructions for treating or preventing a DNA repair protein-deficient cancer in a subject in need thereof. In other embodiments, the at least one compound is selected from the group consisting of N-(4-methoxy-3,5-dimethyl phenyl)-4-(methylthio)benzenesulfonamide (YU126919); 2,3-dichloro-N-(3,4-dimethoxy phenyl)-4-methoxybenzenesulfonamide (YU127190); 5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide (YU128355); 4-methoxy-3-methyl-N-(pyridin-4-ylmethyl) benzenesulfonamide (YU128440); and, N-(4-chlorophenethyl)-4-(((4-methoxyphenyl) sulfonamido)methyl)benzamide (YU175534); and, N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl) benzamide (YU238259).

10 In certain embodiments, the kit further comprises at least one additional antitumor agent. In other embodiments, the at least one compound and at least one additional antitumor agent are coformulated.

The invention further provides a pharmaceutical composition comprising at least one compound, or a salt or solvate thereof, selected from the group consisting of N-(4-methoxy-3,5-dimethyl phenyl)-4-(methylthio)benzenesulfonamide (YU126919); 2,3-dichloro-N-(3,4-dimethoxy phenyl)-4-methoxybenzenesulfonamide (YU127190); 5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide (YU128355); 4-methoxy-3-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (YU128440); and, N-(4-chlorophenethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide (YU175534); and, N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido) methyl)benzamide (YU238259).

In certain embodiments, the pharmaceutical composition further comprises at least one additional antitumor agent, or a salt or solvate thereof. In other embodiments, the at least one compound and at least one additional antitumor agent are coformulated in the same pharmaceutical formulation. In yet other embodiments, the pharmaceutical composition further comprises at least one AKT inhibitor, or a salt or solvate thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

The following detailed description of specific embodiments of the invention will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings specific embodiments. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities of the embodiments shown in the drawings.

Figs. 1A-1D illustrate high-throughput screening reveals a novel class of compounds with synthetic lethality in the context of HDR defects. Fig. 1A illustrates a

methodology of synthetic lethality screen. Fig. 1B illustrates IC₅₀ values for four initial screening hits in cells proficient or deficient in BRCA2 and FANCD2. Fig. 1C illustrates structures of sulfonamide compounds identified in screen of ChemBridge DIVERSet small molecule library or through structural homology screening. Fig. 1D illustrates the structure of YU238259.

Figs. 2A-2D illustrate the finding that the compounds of the invention do not inhibit PARP activity or intercalate into DNA, but decrease HDR efficiency. Fig. 2A is a bar graph illustrating the assessment of PARP activity in presence of diarylsulfonamides by an *in vitro* enzymatic assay. 3-aminobenzamide, a known PARP inhibitor, was a positive control.

Fig. 2B: Plasmid DNA was incubated with either diarylsulfonamides or a known intercalating agent, doxorubicin, and disruption of DNA helical structure was analyzed by circular dichroism spectroscopy. Fig. 2C illustrates a mechanism of DR-GFP and EJ5-GFP cell-based reporter assays for HDR and NHEJ, respectively. Fig. 2D is a bar graph illustrating the effect of YU238259 on frequency of HDR and NHEJ, as assessed by FACS analysis of GFP+ cells.

Figs. 3A-3E illustrate the finding that YU238259 demonstrates synthetic lethality with loss of HDR proteins. Paired, isogenic human cell lines deficient and proficient in (Fig. 3A) BRCA2, (Fig. 3B) ATM, and (Fig. 3C) PTEN were treated with increasing doses of YU238259 for 24 h and toxicity assessed by clonogenic survival assay. Fig. 3D:

Clonogenic survival of A549 cells treated with siRNA against NBS1 or ATRIP for 72 h, reseeded onto 6-well plates, and then treated with YU238259 for 24 h. Fig. 3E: YU238259 showed synthetic lethality to melanoma cells deficient in PTEN, but this was dependent on AKT status. As illustrated, YU238259 showed synthetic lethality to the YURIF melanoma cells that are PTEN mutant and AKT low. But there was only a small effect of YU238259 alone on killing of the YUGEN8 cells (these were PTEN null but had high AKT levels) but a large effect when YU238259 was combined with an AKT inhibitor (MK-2206, or MK2206).

Figs. 4A-4F illustrate the finding that YU238259 exhibits synergism with radiotherapy and DNA-damaging chemotherapy that is potentiated by BRCA2 loss.

Clonogenic assay of DLD-1 and DLD-1 BRCA2-KO cells pretreated with YU238259 for 24 h and then co-treated with (Fig. 4A-4B) ionizing radiation, (Fig. 4C-4D) etoposide, or (Fig. 4E-4F) olaparib for an additional 24 h in the presence of YU238259.

Figs. 5A-5D illustrate the finding that YU238259 inhibits growth of BRCA2-deficient tumor xenografts in nude mice. Growth curves of subcutaneous DLD-1 or DLD-1 BRCA2-KO tumor xenografts in athymic mice treated with (Fig. 5A) four doses of 5 mg/kg

YU128440 or (Fig. 5B) twelve doses of 3 mg/kg Yu238259. Survival rate of mice, as measured by number of days required for tumors to reach 4x their volume at time of treatment, for (Fig. 5C) YU128440 and (Fig. 5D) YU238259.

Figs. 6A-6B illustrate the finding that the mechanism of action of YU238259 appears to involve inhibition of a proximal step in the HDR pathway. Fig. 6A: A549 cells were pretreated with 10 μ M YU238259 for 4 h and then treated with 10 Gy IR. DSB levels were measured by neutral comet assay at 0 h or 24 h post-irradiation. Fig. 6B: Activation of CHK1 and RPA in response to 5 Gy IR or 10 J/m² UV in presence of YU238259 or DMSO vehicle. A549 cells were pretreated with 10 μ M YU238259 for 4 h, irradiated, and allowed to recover for varying amounts of time prior to harvesting and immunoblotting.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates in part to the unexpected discovery of novel compounds that sensitize a tumor cell to anticancer therapies. In certain embodiments, the tumor cell is DNA repair-deficient. In other embodiments, the tumor cell is BRCA2-deficient. In other embodiments, the tumor cell is PTEN-deficient.

Radiation therapy and DNA-damaging chemotherapy are frequently utilized in the treatment of solid tumors, but unfortunately innate or acquired resistance to these therapies remains a major clinical challenge in oncology. The development of small molecules that sensitize tumor cells to established therapies thus represents an attractive approach to extending survival and quality of life in patients. As demonstrated herein, the present invention provides a novel class of DNA double-strand break repair inhibitors that exhibits potent synthetic lethal activity in the setting of DNA damage response and DNA repair defects. The compounds of the invention specifically inhibits homology-dependent DNA repair (HDR), but not non-homologous end-joining (NHEJ), in cell-based GFP reporter assays.

As demonstrated herein, treatment with the compounds of the invention is synergistic with ionizing radiation, etoposide, and PARP inhibition, and that this synergism is heightened in the setting of BRCA2-deficiency. Further, growth of BRCA2-deficient human tumor xenografts in nude mice is significantly delayed by treatment with the compounds of the invention, even in the absence of concomitant DNA-damaging therapy. Without wishing to be limited by any theory, the mechanism of action of this class of small molecules appears to be related to inhibition of a proximal step in the detection and resolution of DNA double-strand breaks (DSBs) via homology-dependent repair. In certain embodiments, the

compounds of the invention are of clinical benefit to patients with advanced BRCA2-negative tumors or PTEN-deficient tumors, either as a monotherapy or as an adjuvant to radiotherapy and certain chemotherapies, or certain targeted therapies that disrupt pro-survival oncogenic pathways such as the AKT pathway (AKT is also known as Protein Kinase B).

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Definitions

Unless defined otherwise, 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. Although any methods and materials similar or equivalent to those
10 described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

As used herein, each of the following terms has the meaning associated with it in this section.

As used herein, the articles “a” and “an” are used to refer to one or to more
15 than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

As used herein, “about,” when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, more preferably $\pm 5\%$, even more preferably $\pm 1\%$, and still more preferably $\pm 0.1\%$
20 from the specified value, as such variations are appropriate to perform the disclosed methods.

A disease or disorder is “alleviated” if the severity of a symptom of the disease or disorder, the frequency with which such a symptom is experienced by a patient, or both, is reduced.

As used herein, the term “antitumor agent” or “chemotherapeutic agent” refers
25 to a compound or composition that may be used to treat or prevent cancer. Non-limiting examples of these agents are DNA damaging agents, such as topoisomerase inhibitors (for example, etoposide, camptothecin, topotecan, irinotecan, teniposide, mitoxantrone), antimicrotubule agents (for example, vincristine, vinblastine and taxanes), antimetabolite agents (for example, cytarabine, methotrexate, hydroxyurea, 5-fluorouracil, fluridine, 6-thioguanine, 6-mercaptopurine, fludarabine, pentostatin, chlorodeoxyadenosine), DNA
30 alkylating agents (for example, cisplatin, mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorumbucil, busulfan, thiotepa, carmustine, lomustine, carboplatin, dacarbazine, procarbazine, temozolomide) and DNA strand break inducing agents (for example, bleomycin, doxorubicin, daunorubicine, idarubicine, mitomycin C).

Antitumor agents include but are not limited to avicin, aclarubicin, acodazole, acronine, adozelesin, adriamycin, aldesleukin, alitretnoin, allopurinol sodium, altretamine, ambomycin, amitantrone acetate, aminoglutethimide, amscrine, anastrozole, annoceous acetogenins, anthramycin, asimicin, asparaginase, asperlin, azacitidine, azetepa, azotomycin, 5 batimstat, benzodepa, bexarotene, bicalutamide, bisantrene, bisanafide, bizelesin, bleomycin, brequinar, brompirimine, bullatacin, busulfan, cabergoline, cactinomycin, calusterone, caracemide, carbetimer, carboplatin, carmustine, carubicin, carzelesin, codefingol, chlorumbucil, celecoxib, cirolemycin, cisplatin, cladribine, crisnatol, cyclophosphamide, cytarabine, dacarbazine, DACA, dactinomycin, daunorubicin, daunomycin, decitabine, 10 denileukine, dexormaplatin, dezaguanine, diaziqone, docetaxel, doxorubicin, droloxifene, dromostalone, duazomycin, edatrexate, eflornithin, elsamitucin, estramustine, etanidazole, etoposide, etoprine, fadrozole, fazarabine, feneretinide, floxuridine, fludarabine, flurouracil, fluorocitabine, 5-FdUMP, fosquidone, fosteuccine, FK-317, FK-973, FR-66979, FR-900482, gemcitabine, gemtuzumab, ozogamicin, Gold Au198, goserelin, guanacone, hydroxyurea, 15 idarubicine, ilmofosine, interferon alpha and analogs, iprolatin, irinotecan, lanreotide, letrozole, leuprolide, liarozole, lometrexol, lomustine, losoxantrone, masoprocol, maytansine, maturedepa, mecholoroethamine, megestrol, melengesterol, melphalan, menogaril, metoprime, mycophenolic acid, mitindomide, mitocarcin, mitogillin, mitomalacin, mitomycin, mitomycin C, mitosper, mitotane, mitoxantrone, nocodazole, nogalamycin, oprelvekin, 20 ormaplatin, proflomycin, oxisuran, paclitaxel, pamidronate, pegaspargase, peliomycin, pentamustin, peplomycin, perfosfamide, pipobroman, piposulfan, piroxantrone, plicamycin, plomestane, porfimer, prednimustin, procarbazine, puromycin, pyrazofurin, riboprime, rogletimide, rituximab, rolliniastatin, safingol, samarium, semustine, simtrazene, sparfosate, sparcomycin, sulphofenur, spirogermanium, spiromustin, spiroplatin, squamocin, 25 squamotacin, streptozocin, streptonigrin, SrCl_2 , talosmycin, taxane, taxoid, tecoglan, temoprofin, tegafur, teloxantrone, teniposide, terxirone, testolactone, thiamiprine, thiotepa, thymitaq, tomudex, tiazofurin, tirapamazine, Top-53, topotecan, toremixifine, trastuzumab, trestolone, tricribine, trimetrexate, tricribine, trimetrexate glucuronate, triptorelin, tubulozole, uracil mustard, valrubicine, uredepa, vapreotide, vinblastin, vincristine, vindesin, vinepidine, 30 zinostatin, vinglycinate, vinleurosine, vinorelbine, vinrosidine, vinzolidine, vorozole, zeniplatin, zorubicine, 2-chlorodeoxyrubicine, 2'-deoxyformycin, CEP-751, raltitrexed, N-propargyl-5,8-dideazafolic acid, 2-chloro-2'-arabino fluoro-2'-deoxyadenosine, 2-chloro-2'-deoxyadenosine, 9-aminocamptothecin anisomycin, trichostatin, hPRL-G129R, linomide, sulfur mustard, N-methyl-N-nitrosourea, fotemustine, streptozotocin, bisplatinum,

temozolomide, mitozolomide, AZQ, ormaplatin, CI-973, DWA2114R, JM216, JM335, tomudex, azacitidine, cytarabine, gemcitabine, 6-mercaptopurine, teniposide, hypoxanthine, doxorubicine, CPT-11, daunorubicine, darubicin, epirubicine, nitrogen mustard, losoxantrone, dicarbazine, amscrine, pyrazoloacridine, all trans retinol, 14-hydroxy-
 5 retro-retinol, all-trans retinoic acid, N-(4-hydroxyphenyl) retinamide, 13-cisretinoic acid, 3-methyl TTNEB, 9-cisretenoic acid, fludarabine, and 2-Cda.

Additional antitumor agents include adecylpenol, 20-epi-1,25-dihydroxyvitamin-D3, 5-ethynyl uracil, abiraterone, aclarubicine, acylfulvene, adozelecin, aldesleukin, ALL-TK antagonists, altretamine, ambumastine, amidox, amifostine, amino
 10 levulinic acid, anagralide, anastrozole, andrographolide, antagonist D, antarelix, anti-dorsalizing morphogenetic protein-1, antiandrogen, antiestrogen, antineoplastone, antisense oligonucleotides, aphidicolin, apoptosis gene modulators, apoptosis regulators, apurinic acid, ara-cdp-dl-PTBA, arginine aminase, asulacrine, atamestine, atrimustine, axinamastine 1 and axinamastine 2, axinamastine 3, azasetron, azatoxin, azatyrosine, baccatin III derivatives,
 15 balanol, BCR/ABL antagonist, benzochlorins, benzoylsaurosporine, beta lactam derivatives, beta-alethine, perillyl alcohol, phenozenomycin, phenyl acetate, phosphatase inhibitors, picibanil, pilocarbine and salts or analogs thereof, pirarubicin, piritrexim, placetin A, placetin B, plasminogen activator inhibitor, platinum complex, phenyl ethyl isothiocyanate and analogs thereof, platinum compounds, platinum triamine complex, podophylotoxin, porfimer
 20 sodium, porphyromycin, propyl bis acridones, mTOR inhibitors, prostaglandins J2, protease inhibitors, protein A based immune modulators, PKB inhibitors PKC inhibitors, microalgal, protein tyrosine phosphatase inhibitors, purine nucleoside phosphorylase inhibitors, purpurins, pyrazoloacridines, pyridoxylated haemoglobin polyoxyethylene conjugate, raf antagonists, raltitrexed, ramosetron, ras farnesyl protein transferase inhibitors, ras inhibitors,
 25 ras-GAP inhibitors, ratelliptine demethylated, Rhenium Re186 etidronate, rhizoxine, ribozyme, RII retinide, rogletimide, rosaglitazone and analogs and derivatives thereof, rohitukine, romurtide, roquinimex, rubiginone B1, ruboxyl, safingol, saintopin, SarCNU, sarcophytol A, sargmostim, sdi 1 mimetics, semustine, senescence derived inhibitor 1, sense oligonucleotide, signal transduction inhibitors, signal transduction modulators, single chain
 30 antigen binding protein, sizofiran, sobuzoxane, sodium borocaptate, sodium phenyl acetate, solverol, somatomedin binding protein, sonermin, sparfosic acid, spicamycin D, spiromustin, splenopentine, spongistatin 1, squalamine, stem cell inhibitor, stem cell division inhibitor, stipiamide, stromelysin, sulfinosine, superactive vasoactive intestinal peptide antagonists, suradista, siramin, swainsonine, synthetic glycosaminoglycans, tallimustine, tamoxifen

methiodide, tauromustine, tazarotene, tacogalan sodium, tegafur, tellurapyrilium, telomerase inhibitors, temoporfin, tmeozolomide, teniposide, tetrachlorodecaoxide, tetrazomine, thaliblastine, thalidomide, thiocoraline, thrombopoetin and mimetics thereof, thymalfasin, thymopoetin receptor agonist, thymotrinan, thyroid stimulating hormone, tin ethyl etiopurpin, 5 tirapazamine, titanocene and salts thereof, topotecan, topsentin, toremifene, totipotent stem cell factors, translation inhibitors, tretinoin, triacetyluridine, tricribine, trimetrexate, triptorelin, tropisetron, turosteride, tyrosine kinase inhibitors, tyrphostins, UBC inhibitors, ubenimex, urogenital sinus derived growth inhibitory factor, urokinase receptor antagonists, vaporeotide, variolin B, vector system, erythrocyte gene therapy, velaresol, veramine, verdins, 10 verteporfin, vinorelbine, vinxaltine, vitaxin, vorozol, zanoterone, zeniplatin, zilascorb and zinostatin.

Additional antitumor agents include antiproliferative agents (*e.g.*, piritrexim isothiocyanate), antiprosthetic hypertrophy agents (sitogluside), Benign prostatic hyperplasia therapy agents (*e.g.*, tomsulosine, RBX2258), prostate growth inhibitory agents (pentomone) 15 and radioactive agents: fibrinogen I125, fludeoxyglucose F18, flurodopa F18, insulin I125, iobenguane I123, iodipamide sodium I131, iodoantipyrine I131, iodocholesterol I131, iodopyracet I125, iofetamine HCL I123, iomethin I131, iomethin I131, iothalamate sodium I125, iothalamate I131, iotyrosine I131, liothyronine I125, merospropril Hg197, methyl iodobenzo guanine (MIBG-I131 or MIBGI123) selenomethionine Se75, technetium Tc99m 20 furifosmin, technetium Tc99m gluceptate, Tc99m biscisate, Tc99m disofenin, TC99m gluceptate, Tc99m lidofenin, Tc99m mebrosfenin, Tc99m medronate and sodium salts thereof, Tc99m mertiatide, Tc99m oxidronate, Tc99m pentetate and salts thereof, Tc99m sestambi, Tc99m siboroxime, Tc99m succimer, Tc99m sulfur colloid, Tc 99m teboroxime, Tc 99m tetrofosmin, Tc99m tiatide, thyroxine I125, thyroxine I131, tolpovidone I131, triolein I125, 25 treoline I125, and treoline I131.

Another category of antitumor agents is anticancer supplementary potentiating agents, *e.g.*, antidepressant drugs (imipramine, desipramine, amitriptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine, and maprotiline), or non-trycyclic anti-depressant drugs (sertaline, trazodone and citalopram), Ca²⁺ antagonists 30 (verapamil, nifedipine, nitrendipine and caroverine), calmodulin inhibitors (prenylamine, trifluoperazine and clomipramine), amphotericin B, triparanol analogs (*e.g.*, tomosifene), antiarrhythmic drugs (*e.g.*, quinidine), antihypertensive drugs (*e.g.*, reserpine), thiol depleters (*e.g.*, buthionine and sulfoximine) and multiple drug resistance reducing agents such as cremaphor EL.

In certain embodiments, antitumor agents include annocetous acetogenins, ascimicin, rolliniastatin, guanocone, squamocin, bullatacin, squamotacin, axanes, baccatin, and taxanes (Paclitaxel and docetaxel).

In certain embodiments, antitumor agents include immune checkpoint inhibitors, such as but not limited to: monoclonal antibodies that target PD-1 and/or PD-L1, such as, but not limited to, pembrolizumab (KEYTRUDA®), lambrolizumab (MK-3475), nivolumab (BMS-936558/MDX-1106/ONO-4538, OPDIVO®), pidilizumab, CT-011, AMP-224, AMP-514, BMS-936559/MDX-1105, MPDL3280A, MSB0010718C and MEDI-4736; monoclonal antibodies that target CTLA-4, such as but not limited to ipilimumab (YERVOY®).

In certain embodiments, antitumor agents include anti-CD20 mAB, rituximab, rituxan, tositumomab, Bexxar, anti-HER2, trastuzumab, Herceptin, MDX20, antiCA125 mAB, antiHE4 mAB, oregovomab mAB, B43.13 mAB, Ovarex, Breva-REX, AR54, GivaRex, ProstaRex mAB, MDX447, gemtuzumab ozogamycin, Mylotarg, CMA-676, anti-CD33 mAB, anti-tissue factor protein, Sunol, IOR-C5, C5, anti-EGFR mAB, Erbitux, anti-IFR1R mAB, MDX-447, anti-17-1A mAB, edrecolomab mAB, Panorex, anti-CD20 mAB (Y-90 labelled), ibritumomab tiuxetan (IDEC-Y2B8), zevalin, and anti-idiotypic mAB.

As used herein, the term “ATM” refers to ataxia telangiectasia mutated.

As used herein, the term “BRCA1” refers to breast cancer 1, early onset.

As used herein, the term “BRCA2” refers to breast cancer 2, early onset.

As used herein, the term “cancer” is defined as disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers include, but are not limited to, breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer, endometrial cancer, glioma, glioblastoma multiforme, neuroblastoma, melanoma, and the like. The term “cancer” as used herein, includes any malignant tumor including, but not limited to, carcinoma (any cancer of epithelial origin) or sarcoma (any mesenchymal neoplasm that arises in bone and soft tissues).

In one aspect, the terms “co-administered” and “co-administration” as relating to a subject refer to administering to the subject a compound of the invention or salt thereof along with a compound that may also treat the disorders or diseases contemplated within the invention. In one embodiment, the co-administered compounds are administered separately,

or in any kind of combination as part of a single therapeutic approach. The co-administered compound may be formulated in any kind of combinations as mixtures of solids and liquids under a variety of solid, gel, and liquid formulations, and as a solution.

As used herein, the term “composition” or “pharmaceutical composition” refers to a mixture of at least one compound useful within the invention with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, transdermal, transmucosal (*e.g.*, sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (*e.g.*, trans- and perivaginally), (intra)nasal and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, pleural, peritoneal, subcutaneous, epidural, otic, intraocular, and/or topical administration.

A “disease” as used herein is a state of health of an animal wherein the animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal’s health continues to deteriorate.

A “disorder” as used herein in an animal is a state of health in which the animal is able to maintain homeostasis, but in which the animal’s state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal’s state of health.

As used herein, the term “DNA repair protein-deficient cell” refers to a cell wherein one or more of the proteins involved in the pathway(s) for DNA repair is absent, expressed at a low level, less active (by virtue of mutation(s), truncation(s), deletion(s), partial inactivation, inhibition by small molecules and/or other proteins, and so forth) or inactive, as compared to a control cell. In certain embodiments, the one or more proteins that is/are absent, expressed at a low level, less active or inactive belongs to the DNA double-strand break (DSB) repair pathway.

As used herein, the terms “effective amount,” “pharmaceutically effective amount” and “therapeutically effective amount” refer to a sufficient amount of an agent to provide the desired biological result. That result may be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term “FANCD2” refers to Fanconi anemia group D2

protein.

“Instructional material,” as that term is used herein, includes a publication, a recording, a diagram, or any other medium of expression that can be used to communicate the usefulness of the composition and/or compound of the invention in a kit. The instructional material of the kit may, for example, be affixed to a container that contains the compound and/or composition of the invention or be shipped together with a container that contains the compound and/or composition. Alternatively, the instructional material may be shipped separately from the container with the intention that the recipient uses the instructional material and the compound and/or composition cooperatively. Delivery of the instructional material may be, for example, by physical delivery of the publication or other medium of expression communicating the usefulness of the kit, or may alternatively be achieved by electronic transmission, for example by means of a computer, such as by electronic mail, or download from a website.

As used herein, “metastasis” refers to the distant spread of a malignant tumor from its site of origin. Cancer cells may metastasize through the bloodstream, through the lymphatic system, across body cavities, or any combination thereof.

As used herein, the term “PALB2” or “FANCN” refers to partner and localizer of BRCA2.

As used herein, “proliferating” and “proliferation” refer to cells undergoing mitosis.

The terms “patient” and “subject” and “individual” are used interchangeably herein, and refer to any animal, or cells thereof whether *in vitro* or *in situ*, amenable to the methods described herein. In a non-limiting embodiment, the patient, subject or individual is a human.

As used herein, the term “pharmaceutically acceptable” refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, *i.e.*, the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the invention within or to the patient such that it may perform its intended function. Typically,

such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation, including the compound useful within the invention, and not injurious to the patient. Some examples of materials that may

5 serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil;

10 glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical

15 formulations.

As used herein, "pharmaceutically acceptable carrier" also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the invention, and are physiologically acceptable to the patient. Supplementary active compounds may also be

20 incorporated into the compositions.

The "pharmaceutically acceptable carrier" may further include a pharmaceutically acceptable salt of the compound useful within the invention. Other additional ingredients that may be included in the pharmaceutical compositions used in the practice of the invention are known in the art and described, for example in Remington's

25 Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As used herein, the language "pharmaceutically acceptable salt" refers to a salt of the administered compound prepared from pharmaceutically acceptable non-toxic acids and bases, including inorganic acids, inorganic bases, organic acids, inorganic bases,

30 solvates, hydrates, and clathrates thereof. Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include sulfate, hydrogen sulfate, hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids (including hydrogen phosphate and dihydrogen phosphate). Appropriate organic acids may be selected from aliphatic, cycloaliphatic,

aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, 5 ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically acceptable base addition salts of compounds of the present invention include, for example, ammonium salts and metallic salts including alkali metal, alkaline earth 10 metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, N,N'-dibenzylethylene-diamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared from the corresponding compound by 15 reacting, for example, the appropriate acid or base with the compound.

The term "prevent," "preventing" or "prevention," as used herein, means avoiding or delaying the onset of symptoms associated with a disease or condition in a subject that has not developed such symptoms at the time the administering of an agent or compound commences.

20 As used herein, the term "PTEN" refers to phosphatase and tensin homolog.

By the term "specifically bind" or "specifically binds," as used herein, is meant that a first molecule preferentially binds to a second molecule (*e.g.*, a particular receptor or enzyme), but does not necessarily bind only to that second molecule.

A "therapeutic" treatment is a treatment administered to a subject who exhibits 25 signs of pathology, for the purpose of diminishing or eliminating those signs.

As used herein, the term "treatment" or "treating" is defined as the application or administration of a therapeutic agent, *i.e.*, a compound of the invention (alone or in combination with another pharmaceutical agent), to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient (*e.g.*, for diagnosis or *ex vivo* applications), who has a condition contemplated herein, a symptom of a condition 30 contemplated herein or the potential to develop a condition contemplated herein, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect a condition contemplated herein, the symptoms of a condition contemplated herein or the potential to develop a condition contemplated herein. Such treatments may be specifically

tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

As used herein, the term “YU126919” refers to N-(4-methoxy-3,5-dimethylphenyl)-4-(methylthio)benzenesulfonamide, or a salt or solvate thereof.

As used herein, the term “YU127190” refers to 2,3-dichloro-N-(3,4-dimethoxyphenyl)-4-methoxybenzenesulfonamide, or a salt or solvate thereof.

As used herein, the term “YU128355” refers to 5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide, or a salt or solvate thereof.

As used herein, the term “YU128440” refers to 4-methoxy-3-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide, or a salt or solvate thereof.

As used herein, the term “YU175534” refers to N-(4-chlorophenethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide, or a salt or solvate thereof.

As used herein, the term “YU238259” refers to N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide, or a salt or solvate thereof.

Throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.1, 5.3, 5.5, and 6. This applies regardless of the breadth of the range.

25 Disclosure

In certain aspects, novel small molecules that exploit common DNA repair deficiencies in tumors and synergize with validated chemotherapeutic agents may provide the basis for rapid clinical translation. To pursue this approach, a synthetic lethality screen was developed to identify small molecules that were preferentially toxic to cells lacking the well-studied repair proteins FANCD2 and BRCA2, but which exhibited low absolute toxicity in isogenic, repair-proficient paired cells.

In a non-limiting example, YU238259 exhibits synthetic lethality in cellular and mouse models of human BRCA2-deficient tumors. YU238259 also demonstrates synergism with ionizing radiation and etoposide, which remain in frequent clinical use.

Analysis of damage-induced phosphorylation of DNA repair proteins suggests that YU238259 acts proximally in the homology-dependent DNA repair pathway. In certain embodiments, this compound acts through inhibition of end resection at the site of DSBs.

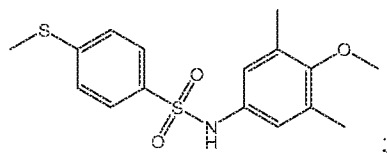
Importantly, YU238259 does not inhibit PARP activity and so offers a novel
 5 mechanism to achieve synthetic lethality with BRCA2 deficiency. Further, the divergent mechanisms of action and low toxicities of PARP inhibition and YU238259 treatment enable them to synergize effectively. Further, the compounds of the invention do not intercalate into DNA and do not inhibit PARP activity.

The observation of synthetic lethality with inactivation of BRCA2, ATM,
 10 FANCD2, and PTEN underscores the potential clinical utility of YU238259 across a variety of common tumors. Of note, BRCA1/2 mutations account for 5-13% of ovarian cancers in developed countries and are associated with higher histologic grade and poorer prognosis. Approximately 60% of ovarian cancers are metastatic at the time of diagnosis. For these stage III and IV ovarian carcinomas, therapeutic options are limited and five-year survival
 15 rates are low. The data presented herein show increased cytotoxicity of YU238259 in the patient-derived BRCA2-deficient ovarian carcinoma line PEO1 relative to its treatment-resistant, BRCA2-wild-type equivalent, PEO4. Given the need for more effective chemotherapy and the striking lethality of ovarian cancer, novel synthetic lethal agents such as YU238259 that synergize with other emerging therapies, such as olaparib, have significant
 20 clinical potential in this setting.

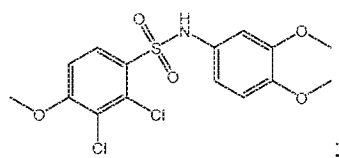
Compounds and Compositions

In certain embodiments, the compounds of the invention, or a salt or solvate thereof, comprise:

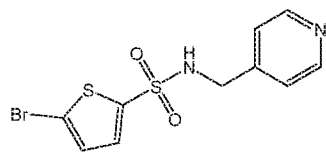
25 N-(4-methoxy-3,5-dimethyl phenyl)-4-(methylthio)benzenesulfonamide (YU126919)



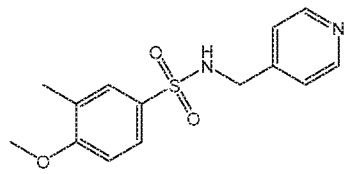
2,3-dichloro-N-(3,4-dimethoxy phenyl)-4-methoxybenzenesulfonamide (YU127190)



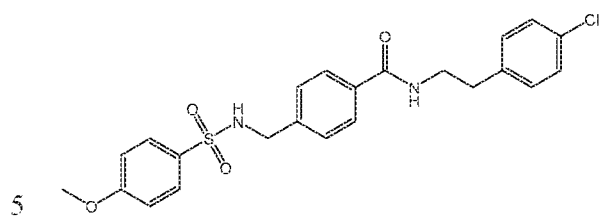
5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide (YU128355)



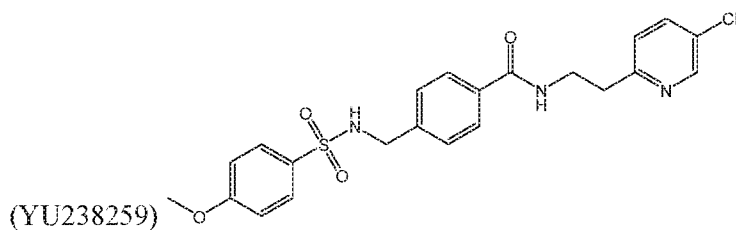
4-methoxy-3-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (YU128440)



N-(4-chlorophenethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide (YU175534)



N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl) benzamide



and any mixtures thereof.

Pharmaceutical compositions comprising at least one compound of the invention, as well as at least one pharmaceutically acceptable carrier, are also contemplated in the invention. Pharmaceutical compositions comprising at least one compound of the invention and at least one additional antitumor agent, as well as at least one pharmaceutically acceptable carrier, are also contemplated in the invention.

15 Methods

The invention includes a method of treating or preventing a DNA repair protein-deficient cancer in a subject in need thereof.

In certain embodiments, the method comprises administering to the subject a therapeutically effective amount of at least one compound, or a salt or solvate thereof, selected from the group consisting of N-(4-methoxy-3,5-dimethyl phenyl)-4-(methylthio) benzenesulfonamide (YU126919), 2,3-dichloro-N-(3,4-dimethoxy phenyl)-4-

methoxybenzene sulfonamide (YU127190), 5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide (YU128355), 4-methoxy-3-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (YU128440), N-(4-chlorophenethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide (YU175534), and, N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide (YU238259), whereby the cancer is treated or prevented in the subject.

In certain embodiments, the at least one compound inhibits DNA double strand break repair in the cancer. In other embodiments, the at least one compound inhibits homology-dependent DNA repair in the cancer. In yet other embodiments, the cancer is deficient in at least one protein selected from the group consisting of BRCA1, BRCA2, PTEN, ATM, PALB2, FANCD2, RAD51, RAD51 paralogs, or other component of the homology dependent DNA repair pathway or the non-homologous end joining pathway. In yet other embodiments, the cancer is deficient in BRCA2.

In certain embodiments, the subject is further administered at least one additional antitumor agent. In other embodiments, the antitumor agent is selected from the group consisting of topoisomerase inhibitors; alkylating agents; nitrosoureas; antimetabolites; antitumor antibiotics; antimicrotubule agents; hormonal agents; DNA strand break inducing agents; EGF receptor inhibitors and anti-EGF receptor antibodies; AKT inhibitors; mTOR inhibitors; CDK inhibitors; receptor tyrosine kinase (RTK) inhibitors; ribonucleotide reductase inhibitors; immune checkpoint inhibitors; and miscellaneous agents. In yet other embodiments, administration of the at least one compound and at least one additional antitumor agent is synergistic. In yet other embodiments, the at least one compound and at least one additional antitumor agent are coadministered to the subject. In yet other embodiments, the at least one compound and at least one additional antitumor agent are coformulated.

In certain embodiments, the subject is further administered radiation therapy. In other embodiments, administration of the at least one compound and the radiation therapy is synergistic.

In certain embodiments, the at least one compound is administered to the subject through a route selected from the group consisting of oral, transdermal, transmucosal, intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, pleural, peritoneal, subcutaneous, epidural, otic, intraocular, and topical.

In certain embodiments, the cancer comprises breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal

cancer, liver cancer, brain cancer, glioma, glioblastoma multiforme, melanoma, lymphoma, leukemia, lung cancer, endometrial cancer, head and neck cancer, sarcoma, multiple myeloma and/or neuroblastoma. In other embodiments, the cancer comprises breast cancer.

In certain embodiments, the subject is a mammal. In other embodiments, the mammal is a human.

Kits

The invention includes a kit comprising at least a compound of the invention, an applicator, and an instructional material for use thereof. The instructional material included in the kit comprises instructions for preventing or treating a DNA repair protein-deficient cancer contemplated within the invention in a subject. The instructional material recites the amount of, and frequency with which, the at least one compound of the invention should be administered to the subject. In other embodiments, the kit further comprises at least one additional antitumor agent.

Combination Therapies

In certain embodiments, the compounds of the invention are useful in the methods of the invention in combination with at least one additional antitumor compound. This additional compound may comprise compounds identified herein or compounds, *e.g.*, commercially available compounds, known to treat, prevent or reduce the symptoms of cancer.

In one aspect, the present invention contemplates that a compound useful within the invention may be used in combination with a therapeutic agent such as an antitumor agent, including but not limited to a chemotherapeutic agent, an anti-cell proliferation agent or any combination thereof.

For example, any conventional chemotherapeutic agents of the following non-limiting exemplary classes are included in the invention: topoisomerase inhibitors; alkylating agents; nitrosoureas; antimetabolites; antitumor antibiotics; antimicrotubule agents; hormonal agents; DNA strand break inducing agents; EGF receptor inhibitors and anti-EGF receptor antibodies; AKT inhibitors; mTOR inhibitors; CDK inhibitors; receptor tyrosine kinase (RTK) inhibitors; ribonucleotide reductase inhibitors; and miscellaneous agents.

Topoisomerase inhibitors include etoposide, camptothecin, topotecan, irrinotecan, teniposide, and mitoxantrone.

Alkylating agents are so named because of their ability to add alkyl groups to

many electronegative groups under conditions present in cells, thereby interfering with DNA replication to prevent cancer cells from reproducing. Most alkylating agents are cell cycle non-specific. In specific aspects, they stop tumor growth by cross-linking guanine bases in DNA double-helix strands. Non-limiting examples include busulfan, carboplatin, 5 chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, mechlorethamine hydrochloride, melphalan, procarbazine, thiotepa, and uracil mustard.

Antimetabolites prevent incorporation of bases into DNA during the synthesis (S) phase of the cell cycle, prohibiting normal development and division. Non limiting examples of antimetabolites include drugs such as 5-fluorouracil, 6 mercaptopurine, 10 capecitabine, cytosine arabinoside, floxuridine, fludarabine, gemcitabine, methotrexate, and thioguanine.

Antitumor antibiotics generally prevent cell division by interfering with enzymes needed for cell division or by altering the membranes that surround cells. Included in this class are the anthracyclines, such as doxorubicin, which act to prevent cell division by 15 disrupting the structure of the DNA and terminate its function. These agents are cell cycle non-specific. Non-limiting examples of antitumor antibiotics include dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin-C, and mitoxantrone.

Antimicrotubule agents include plant alkaloids that inhibit or stop mitosis or inhibit enzymes that prevent cells from making proteins needed for cell growth. Frequently 20 used plant alkaloids include vinblastine, vincristine, vindesine, and vinorelbine. However, the invention should not be construed as being limited solely to these plant alkaloids. The taxanes affect cell structures called microtubules that are important in cellular functions. In normal cell growth, microtubules are formed when a cell starts dividing, but once the cell stops dividing, the microtubules are disassembled or destroyed. Taxanes prohibit the 25 microtubules from breaking down such that the cancer cells become so clogged with microtubules that they cannot grow and divide. Non-limiting exemplary taxanes include paclitaxel and docetaxel.

Hormonal agents and hormone-like drugs are utilized for certain types of cancer, including, for example, leukemia, lymphoma, and multiple myeloma. They are often 30 employed with other types of chemotherapy drugs to enhance their effectiveness. Sex hormones are used to alter the action or production of female or male hormones and are used to slow the growth of breast, prostate, and endometrial cancers. Inhibiting the production (aromatase inhibitors) or action (tamoxifen) of these hormones can often be used as an adjunct to therapy. Some other tumors are also hormone dependent. Tamoxifen is a non-

limiting example of a hormonal agent that interferes with the activity of estrogen, which promotes the growth of breast cancer cells.

DNA strand break inducing agents include bleomycin, doxorubicine, daunorubicine, idarubicine, and mitomycin.

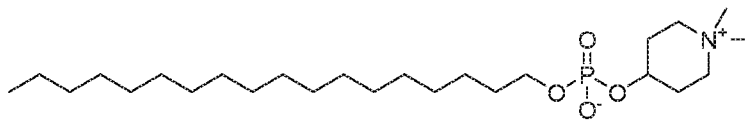
5 Miscellaneous agents include chemotherapeutics such as hydroxyurea, L-asparaginase, and procarbazine that are also useful in the invention.

An anti-cell proliferation agent can further be defined as an apoptosis-inducing agent or a cytotoxic agent. The apoptosis-inducing agent may be a granzyme, a Bcl-2 family member, cytochrome C, a caspase, or a combination thereof. Exemplary granzymes include
 10 granzyme A, granzyme B, granzyme C, granzyme D, granzyme E, granzyme F, granzyme G, granzyme H, granzyme I, granzyme J, granzyme K, granzyme L, granzyme M, granzyme N, or a combination thereof. In other specific aspects, the Bcl-2 family member is, for example, Bax, Bak, Bcl-Xs, Bad, Bid, Bik, Hrk, Bok, or a combination thereof.

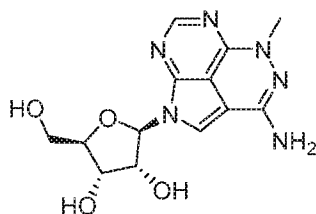
In certain embodiments, the caspase is caspase-1, caspase-2, caspase-3,
 15 caspase-4, caspase-5, caspase-6, caspase-7, caspase-8, caspase-9, caspase-10, caspase-11, caspase-12, caspase-13, caspase-14, or a combination thereof. In other embodiments, the cytotoxic agent is TNF- α , gelonin, Prodigiosin, a ribosome-inhibiting protein (RIP), Pseudomonas exotoxin, Clostridium difficile Toxin B, Helicobacter pylori VacA, Yersinia enterocolitica YopT, Violacein, diethylenetriaminepentaacetic acid, irofulven, Diphtheria
 20 Toxin, mitogillin, ricin, botulinum toxin, cholera toxin, saporin 6, or a combination thereof.

In another aspect, the present invention contemplates that a compound useful within the invention may be used in combination with an AKT inhibitor, such as but not limited to:

perifosine (also known as N,N'-dimethylpiperidinium-4-yl(octadecyl)phosphate; or
 25 1,1-dimethyl-4-[[[(octadecyloxy)hydroxyphosphoryl]oxy]piperidinium inner salt):

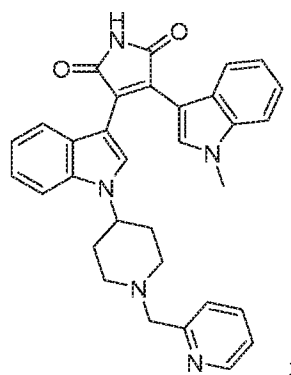


tricitriline or the 5'-phosphate thereof (also known as (2S,3R,4S,5R)-2-(3-amino-5-methyl-1,4,5,6,8-pentaazaacenaphthylene-1(5H)-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol; or 3-amino-5-methyl-1-(beta-D-ribofuranosyl)-1,5-dihydro-1,4,5,6,8-
 30 pentaazaacenaphthylene):

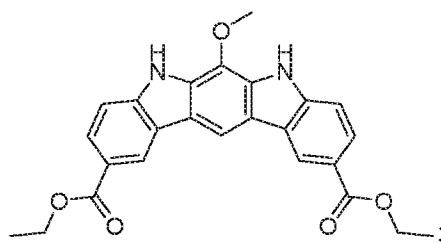


GBC-590 (also known as GCS-100, GCS-100LE or LJPC-101; naturally occurring complex polysaccharide derived from pectin);

enzastaurin (also known as 3-(1-methyl-1H-indol-3-yl)-4-[1-[1-(pyridin-2-ylmethyl) piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole-2,5-dione):

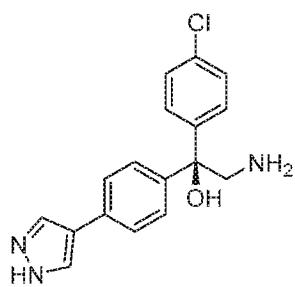


SR-13668 (also known as 6-methoxy-5,7-dihydroindolo[2,3-b]carbazole-2,10-dicarboxylic acid diethyl ester):

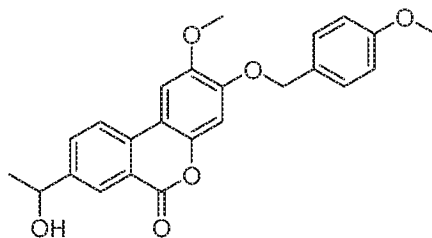


10 apelin (MNLRLCVQAL LLLWLSLTAV CGGSLMPLPD GNGLEDGNVR
HLVQPRGSRN GPGPWQGGRR KFRQRPRLS HKGPMPPF; SEQ ID NO: 1);

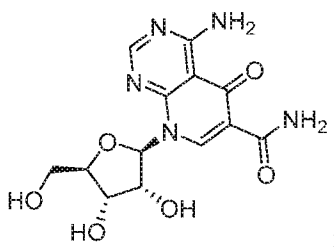
AT-13148 (also known as 2-amino-1(S)-(4-chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl] ethanol):



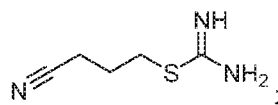
P-529 (also known as 8-(1-hydroxyethyl)-2-methoxy-3-(4-methoxybenzyloxy)-6H-dibenzo[b,d]pyran-6-one):



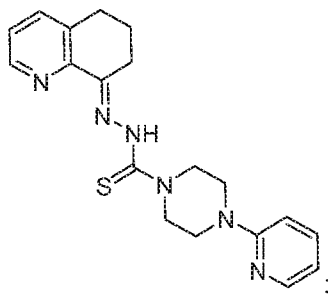
AKT-SII (also known as 4-amino-8-(beta-D-ribofuranosyl)-5-oxo-5,8-dihydropyrido [2,3-d]pyrimidine-6-carboxamide):



S-(3-Cyanopropyl)isothiourea hydrochloride (also known as thioureidobutyronitrile):

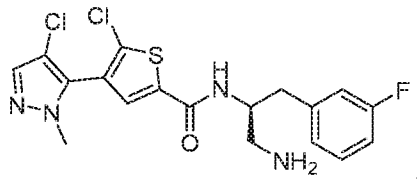


N'-(5,6,7,8-Tetrahydroquinolin-8-ylidene)-4-(2-pyridyl)piperazine-1-

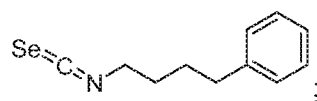
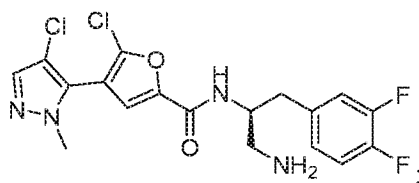


carbothiohydrazide:

afuresertib (also known as N-[2-amino-1(S)-(3-fluorobenzyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)thiophene-2-carboxamide):

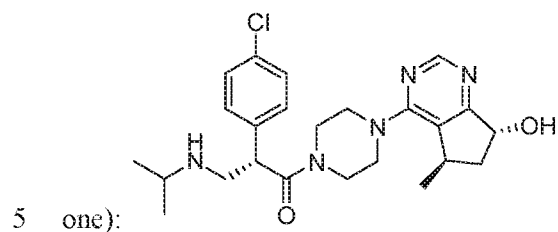


uprosertib (also known as N-[(2S)-1-amino-3-(3,4-difluorophenyl)propan-2-yl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furamide):



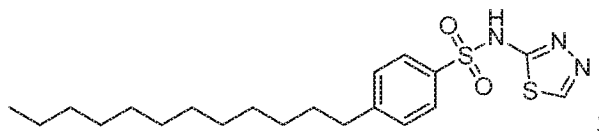
(4-isoselenocyanatobutyl)benzene:

ipatasertib (also known as 2(S)-(4-Chlorophenyl)-1-[4-[7(R)-hydroxy-5(R)-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl]piperazin-1-yl]-3-(isopropylamino)propan-1-

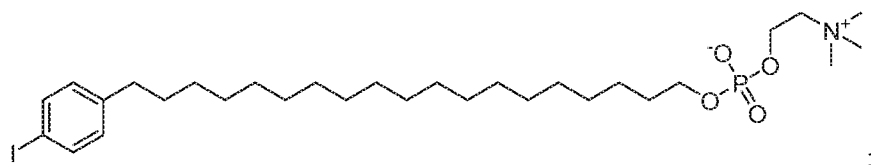


5 one):

4-dodecyl-N-(1,3,4-thiadiazol-2-yl)benzenesulfonamide:

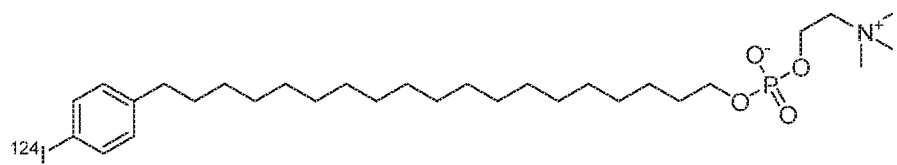


18-(4-Iodophenyl)octadecylphosphocholine:

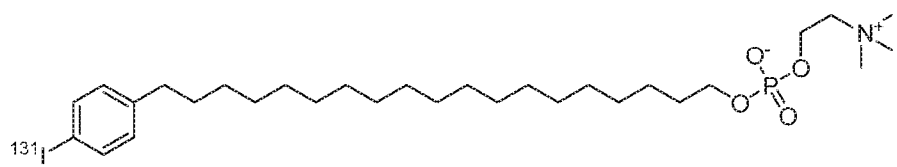


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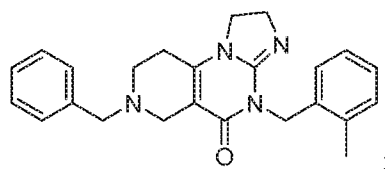
18-(4-[¹²⁴I]Iodophenyl)octadecylphosphocholine:



18-(4-[¹³¹I]Iodophenyl)octadecylphosphocholine:

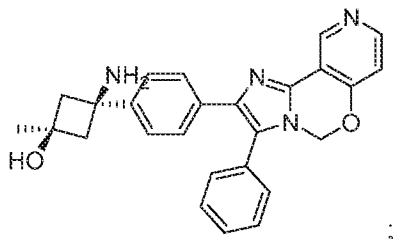


7-benzyl-4-(2-methylbenzyl)-2,4,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]



pyrimidin-5(1H)-one:

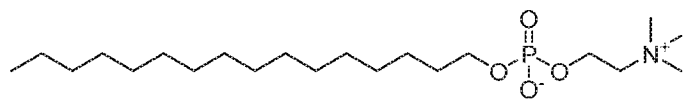
trans-3-amino-1-methyl-3-[4-(3-phenylimidazo[1,2-c]pyrido[3,4-c][1,3]oxazin-2-



yl)phenyl]cyclobutanol:

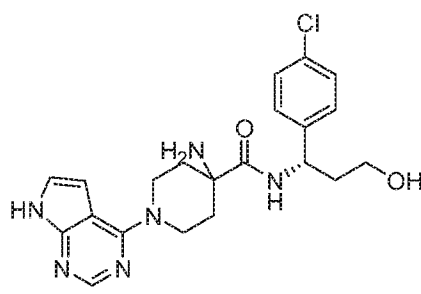
miltefosine (also known as 2-(hexadecoxy-oxido-phosphoryl)oxyethyl-trimethyl-

5 azanium):

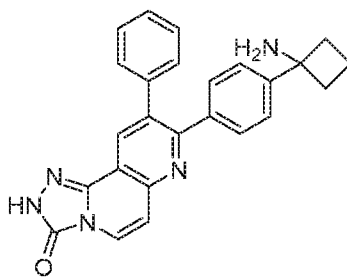


AZD5363 (also known as 4-amino-N-[(1S)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-

(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidine-4-carboxamide):



10 MK-2206 (also known as 8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl-2H-[1,2,4]triazolo[3,4-f][1,6]naphthyridin-3-one):

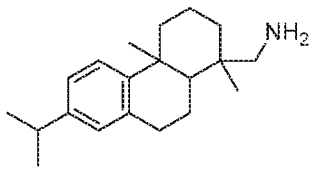


ABTL-0812 (Ability Pharmaceuticals; Lipopharma);

ALM-301 (Almac Discovery);

15 ARQ-092 (Arqule);

a nanoliposomal formulation of leelamine (also known as 1,4a-dimethyl-7-isopropyl-1,2,3,4,4a,9,10,10a-octahydro-1-phenanthrenemethylamine; Nanolipolee-007; Melanovus);



BAY-1125976 (Bayer);

5 MSC-2363318A (EMD Serono);

a salt or solvate thereof, or any mixtures thereof.

A synergistic effect may be calculated, for example, using suitable methods such as, for example, the Sigmoid- $E_{\max}$ equation (Holford & Scheiner, 19981, Clin. Pharmacokinet. 6: 429-453), the equation of Loewe additivity (Loewe & Muischnek, 1926, 10 Arch. Exp. Pathol Pharmacol. 114: 313-326) and the median-effect equation (Chou & Talalay, 1984, Adv. Enzyme Regul. 22:27-55). Each equation referred to above may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, 15 respectively.

Administration/Dosage/Formulations

The regimen of administration may affect what constitutes an effective amount. The therapeutic formulations may be administered to the subject either prior to or 20 after the onset of a disease or disorder contemplated in the invention. Further, several divided dosages, as well as staggered dosages may be administered daily or sequentially, or the dose may be continuously infused, or may be a bolus injection. Further, the dosages of the therapeutic formulations may be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

25 Administration of the compositions of the present invention to a patient, preferably a mammal, more preferably a human, may be carried out using known procedures, at dosages and for periods of time effective to treat a disease or disorder contemplated in the invention. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the state of the disease or disorder in 30 the patient; the age, sex, and weight of the patient; and the ability of the therapeutic compound to treat a disease or disorder contemplated in the invention. Dosage regimens may

be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention is from about 1 and 5,000 mg/kg of body weight/per day. One of ordinary skill in the art would be able to study the relevant factors and make the determination regarding the effective amount of the therapeutic compound without undue experimentation.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The therapeutically effective amount or dose of a compound of the present invention depends on the age, sex and weight of the patient, the current medical condition of the patient and the progression of a disease or disorder contemplated in the invention.

A medical doctor, *e.g.*, physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

A suitable dose of a compound of the present invention may be in the range of from about 0.01 mg to about 5,000 mg per day, such as from about 0.1 mg to about 1,000 mg, for example, from about 1 mg to about 500 mg, such as about 5 mg to about 250 mg per day. The dose may be administered in a single dosage or in multiple dosages, for example from 1 to 4 or more times per day. When multiple dosages are used, the amount of each dosage may be the same or different. For example, a dose of 1 mg per day may be administered as two 0.5 mg doses, with about a 12-hour interval between doses.

Compounds of the invention for administration may be in the range of from about 1 µg to about 10,000 mg, about 20 µg to about 9,500 mg, about 40 µg to about 9,000 mg, about 75 µg to about 8,500 mg, about 150 µg to about 7,500 mg, about 200 µg to about 7,000 mg, about 3050 µg to about 6,000 mg, about 500 µg to about 5,000 mg, about 750 µg to about 4,000 mg, about 1 mg to about 3,000 mg, about 10 mg to about 2,500 mg, about 20 mg to about 2,000 mg, about 25 mg to about 1,500 mg, about 30 mg to about 1,000 mg, about

40 mg to about 900 mg, about 50 mg to about 800 mg, about 60 mg to about 750 mg, about 70 mg to about 600 mg, about 80 mg to about 500 mg, and any and all whole or partial increments there between.

In some embodiments, the dose of a compound of the invention is from about
5 1 mg and about 2,500 mg. In some embodiments, a dose of a compound of the invention used in compositions described herein is less than about 10,000 mg, or less than about 8,000 mg, or less than about 6,000 mg, or less than about 5,000 mg, or less than about 3,000 mg, or less than about 2,000 mg, or less than about 1,000 mg, or less than about 500 mg, or less than about 200 mg, or less than about 50 mg. Similarly, in some embodiments, a dose of a second
10 compound as described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less
15 than about 2 mg, or less than about 1 mg, or less than about 0.5 mg, and any and all whole or partial increments thereof.

In one embodiment, the compositions of the invention are administered to the patient in dosages that range from one to five times per day or more. In another embodiment, the compositions of the invention are administered to the patient in range of dosages that
20 include, but are not limited to, once every day, every two, days, every three days to once a week, and once every two weeks. It is readily apparent to one skilled in the art that the frequency of administration of the various combination compositions of the invention varies from individual to individual depending on many factors including, but not limited to, age, disease or disorder to be treated, gender, overall health, and other factors. Thus, the invention
25 should not be construed to be limited to any particular dosage regime and the precise dosage and composition to be administered to any patient is determined by the attending physical taking all other factors about the patient into account.

It is understood that the amount of compound dosed per day may be administered, in non-limiting examples, every day, every other day, every 2 days, every 3
30 days, every 4 days, or every 5 days. For example, with every other day administration, a 5 mg per day dose may be initiated on Monday with a first subsequent 5 mg per day dose administered on Wednesday, a second subsequent 5 mg per day dose administered on Friday, and so on.

In the case wherein the patient's status does improve, upon the doctor's

discretion the administration of the compound of the invention is optionally given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a “drug holiday”). The length of the drug holiday optionally varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday includes from 10%-100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is reduced, as a function of the disease or disorder, to a level at which the improved disease is retained. In one embodiment, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

The compounds for use in the method of the invention may be formulated in unit dosage form. The term “unit dosage form” refers to physically discrete units suitable as unitary dosage for patients undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form may be for a single daily dose or one of multiple daily doses (*e.g.*, about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form may be the same or different for each dose.

Toxicity and therapeutic efficacy of such therapeutic regimens are optionally determined in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD₅₀ and ED₅₀. The data obtained from cell culture assays and animal studies are optionally used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage optionally varies within this range depending upon the dosage form employed and the route of administration utilized.

In one embodiment, the compositions of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the

pharmaceutical compositions of the invention comprise a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier.

The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal and the like. In many cases, it is preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition.

In one embodiment, the present invention is directed to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a compound of the invention, alone or in combination with a second pharmaceutical agent; and instructions for using the compound to treat, prevent, or reduce one or more symptoms of a disease or disorder contemplated in the invention.

Formulations may be employed in admixtures with conventional excipients, *i.e.*, pharmaceutically acceptable organic or inorganic carrier substances suitable for any suitable mode of administration, known to the art. The pharmaceutical preparations may be sterilized and if desired mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. They may also be combined where desired with other active agents, *e.g.*, analgesic agents.

Suitable compositions and dosage forms include, for example, dispersions, suspensions, solutions, syrups, granules, beads, powders, pellets, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, and the like. It should be understood that the formulations and compositions that would be useful in the present invention are not limited to the particular formulations and compositions that are described herein.

30 *Oral Administration*

For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically

excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

For oral administration, the compounds may be in the form of tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, polyvinylpyrrolidone, hydroxypropylcellulose or hydroxypropylmethylcellulose); fillers (*e.g.*, cornstarch, lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.*, magnesium stearate, talc, or silica); disintegrates (*e.g.*, sodium starch glycollate); or wetting agents (*e.g.*, sodium lauryl sulphate). If desired, the tablets may be coated using suitable methods and coating materials such as OPADRY™ film coating systems available from Colorcon, West Point, Pa. (*e.g.*, OPADRY™ OY Type, OYC Type, Organic Enteric OY-P Type, Aqueous Enteric OY-A Type, OY-PM Type and OPADRY™ White, 32K18400). Liquid preparation for oral administration may be in the form of solutions, syrups or suspensions. The liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.*, methyl or propyl p-hydroxy benzoates or sorbic acid).

Granulating techniques are well known in the pharmaceutical art for modifying starting powders or other particulate materials of an active ingredient. The powders are typically mixed with a binder material into larger permanent free-flowing agglomerates or granules referred to as a “granulation.” For example, solvent-using “wet” granulation processes are generally characterized in that the powders are combined with a binder material and moistened with water or an organic solvent under conditions resulting in the formation of a wet granulated mass from which the solvent must then be evaporated.

Melt granulation generally consists in the use of materials that are solid or semi-solid at room temperature (*i.e.* having a relatively low softening or melting point range) to promote granulation of powdered or other materials, essentially in the absence of added water or other liquid solvents. The low melting solids, when heated to a temperature in the melting point range, liquefy to act as a binder or granulating medium. The liquefied solid spreads itself over the surface of powdered materials with which it is contacted, and on

cooling, forms a solid granulated mass in which the initial materials are bound together. The resulting melt granulation may then be provided to a tablet press or be encapsulated for preparing the oral dosage form. Melt granulation improves the dissolution rate and bioavailability of an active (*i.e.*, drug) by forming a solid dispersion or solid solution.

5 U.S. Patent No. 5,169,645 discloses directly compressible wax-containing granules having improved flow properties. The granules are obtained when waxes are admixed in the melt with certain flow improving additives, followed by cooling and granulation of the admixture. In certain embodiments, only the wax itself melts in the melt combination of the wax(es) and additives(s), and in other cases both the wax(es) and the
10 additives(s) will melt.

The present invention also includes a multi-layer tablet comprising a layer providing for the delayed release of one or more compounds of the invention, and a further layer providing for the immediate release of a medication for treatment of a disease or disorder. Using a wax/pH-sensitive polymer mix, a gastric insoluble composition may be
15 obtained in which the active ingredient is entrapped, ensuring its delayed release.

Parenteral Administration

For parenteral administration, the compounds may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose and/or continuous infusion. Solutions, suspensions or
20 emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing and/or dispersing agents may be used.

Additional Administration Forms

Additional dosage forms of this invention include dosage forms as described in U.S. Patents Nos. 6,340,475, 6,488,962, 6,451,808, 5,972,389, 5,582,837, and 5,007,790.
25 Additional dosage forms of this invention also include dosage forms as described in U.S. Patent Applications Nos. 2003/0147952, 2003/0104062, 2003/0104053, 2003/0044466, 2003/0039688, and 2002/0051820. Additional dosage forms of this invention also include dosage forms as described in PCT Applications Nos. WO 03/35041, WO 03/35040, WO 03/35029, WO 03/35177, WO 03/35039, WO 02/96404, WO 02/32416, WO 01/97783, WO
30 01/56544, WO 01/32217, WO 98/55107, WO 98/11879, WO 97/47285, WO 93/18755, and WO 90/11757.

Controlled Release Formulations and Drug Delivery Systems

In certain embodiments, the formulations of the present invention may be, but are not limited to, short-term, rapid-offset, as well as controlled, for example, sustained

release, delayed release and pulsatile release formulations.

The term sustained release is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that may, although not necessarily, result in substantially constant blood levels of a drug over
5 an extended time period. The period of time may be as long as a month or more and should be a release which is longer than the same amount of agent administered in bolus form.

For sustained release, the compounds may be formulated with a suitable polymer or hydrophobic material which provides sustained release properties to the compounds. As such, the compounds for use the method of the invention may be
10 administered in the form of microparticles, for example, by injection or in the form of wafers or discs by implantation.

In certain embodiments, the compounds of the invention are administered to a patient, alone or in combination with another pharmaceutical agent, using a sustained release formulation.

15 The term delayed release is used herein in its conventional sense to refer to a drug formulation that provides for an initial release of the drug after some delay following drug administration and that may, although not necessarily, include a delay of from about 10 min up to about 12 hours.

The term pulsatile release is used herein in its conventional sense to refer to a
20 drug formulation that provides release of the drug in such a way as to produce pulsed plasma profiles of the drug after drug administration.

The term immediate release is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

As used herein, short-term refers to any period of time up to and including
25 about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 min, about 20 min, or about 10 min and any or all whole or partial increments thereof after drug administration after drug administration.

As used herein, rapid-offset refers to any period of time up to and including
30 about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 min, about 20 min, or about 10 min, and any and all whole or partial increments thereof after drug administration.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents were considered to be within the

scope of this invention and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, *e.g.*, nitrogen atmosphere, and reducing/oxidizing agents, with art-
5 recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges,
10 as well as the upper or lower limits of a range of values, are also contemplated by the present application.

The following examples further illustrate aspects of the present invention. However, they are in no way a limitation of the teachings or disclosure of the present invention as set forth herein.

15

EXAMPLES

The invention is now described with reference to the following Examples. These Examples are provided for the purpose of illustration only and the invention should in no way be construed as being limited to these Examples, but rather should be construed to
20 encompass any and all variations which become evident as a result of the teaching provided herein.

Materials and Methods

25 *Chemicals:*

Etoposide (4'-Demethyl-epipodophyllotoxin 9-[4,6-O-(R)-ethylidene-beta-D-glucopyranoside], 4' -(dihydrogen phosphate), or a salt or solvate thereof), doxorubicin ((7S,9S)-7-[(2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione, or a salt or solvate
30 thereof), caffeine, and mirin were purchased from Sigma.

Olaparib (4-[(3-[(4-cyclopropylcarbonyl)piperazin-4-yl]carbonyl)-4-fluorophenyl]methyl(2H)phthalazin-1-one, or a salt or solvate thereof) and VE-821 (3-amino-6-[4-(methylsulfonyl)phenyl]-N-phenyl-2-Pyrazinecarboxamide, or a salt or solvate thereof), were purchased from Selleck.

Cell lines:

DLD-1 and DLD-1 BRCA2-KO human colorectal adenocarcinoma cell lines (Horizon Discovery, Cambridge, UK) were cultured in McCoy's 5A medium with 10% FBS.

5 PEO1/4 cells (Sakai, *et al.*, 2009, Cancer Res. 69(16):6381-6386) were a gift of Dr. Toshiyasu Tanaguchi. U251+vector and U251+PTEN cells were a gift of Dr. Amit Maity. HCC1937+vector and HCC1937+BRCA1 cells were a gift of Dr. Zhong Yun. U2OS cell lines with integrated reporters (DR-GFP and EJ5-GFP) have been described previously (Gunn & Stark, 2012, Methods Mol. Biol. 920:379-391; Pierce, *et al.*, 1999, Genes & Dev.

10 13(20):2633-2638). GM05849 and GM05849+ATM cells have been described previously. A549 cells were from ATCC. PD20 and PD20+FANCD2 cells were from the OHSU FA Cell Repository and were grown in MEM-alpha with 15% FBS. YURIF and YUGEN8 primary human melanoma lines were obtained from the Yale SPORC in Skin Cancer and were cultured in Opti-MEM supplemented with 5% FBS. All other cell lines were cultured in

15 DMEM with 10% FBS.

Screening libraries:

ChemBridge DIVERSet and other small molecule libraries were formatted as 10 mM DMSO stocks in 384-well plates. For diarylsulfonamide dose response curves, 100

20 mM stocks were prepared and serially diluted by 2-fold in DMSO.

Synthetic lethality screening assay:

Cells were seeded in 20 μ L media onto white clear-bottom 384-well plates (Corning) using a MultiDrop Combi Reagent Dispenser (Thermo Scientific). Primary

25 screening used PD20 $\pm$ FANCD2 cells plated at 750 cells/well. Follow-up screening and dose response curves used PEO1 and PEO4 cells plated at 750 and 1500 cells/well, respectively. After seeding, the assay plates were centrifuged at 500 rpm for 10 seconds and incubated overnight. 20 nL compound was then transferred from the source plate to the assay plates using an Aquarius (Tecan) with a 384-well pin tool (V&P Scientific). Final

30 concentration of screening compounds was 10 μ M in 0.1% DMSO. Tamoxifen (final conc. 30 μ M for PD20 cells and 60 μ M for PEO1/4 cells) was added to positive control wells. Assay plates were centrifuged at 500 rpm for 10 seconds and then incubated for 72 h. CellTiter-Glo (Promega) was used to measure cell viability in the assay wells according to

the manufacturer's instructions. 20 μ L/well of CellTiter-Glo was added to each assay plate using a MultiDrop Combi. Plates were shaken on a Thermomixer R (Eppendorf) at 1100 rpm for 1 minute and incubated in the dark for 10 minutes at room temperature. Luminescence was measured using an Envision plate reader (PerkinElmer) with 0.3 second sampling time
5 per well.

PARP enzymatic assay:

PARP activity was assessed using a Universal PARP Chemiluminescent Assay (Trevigen) according to the manufacturer's instructions. 3-aminobenzamide served as
10 a positive control for PARP inhibition.

Neutral comet assay:

A549 cells were treated with 10 μ M YU238259 for 4 hours and then received 10 Gy IR. Cells were then harvested either immediately or 24 h post-irradiation and a neutral
15 comet assay was performed per manufacturer's instructions (Trevigen). Comet tail moments were analyzed using CometScore software (TriTek) for at least 50 randomly chosen cells per condition. Error bars represent standard deviations (SDs).

Clonogenic survival assays:

20 Cells were seeded into 6-well plates at densities of 500-1000 cells/well, incubated overnight, and then treated with YU238259 for 48 hours, after which fresh cell media was added. For synergism assays, cells were treated with YU238259 for 24 h, then irradiated or treated with etoposide, olaparib, or cisplatin. Cells were incubated with all drugs for another 24 h prior to addition of untreated media. All dose combinations were
25 performed in triplicate. Errors bars represent SDs.

DSB repair reporter assays:

U2OS reporter cell lines (DR-GFP or EJ5-GFP) were pretreated in triplicate with varying concentrations of YU238259 for 24 h, after which 4 μ g of SCE-I plasmid was
30 transfected into 1×10^6 cells/replicate using an Amaxa Nucleofector (Lonza). Transfected cells were reseeded on 6-well plates and cultured with YU238259 for an additional 72 h. The percentage of GFP-positive cells was quantified by flow cytometry. Data analysis was performed using FlowJo software (Tree Star Inc.). Error bars represent SDs.

Mouse tumor xenografts:

069(nu)/070(nu/+) athymic nude mice were purchased from Harlan. At 4-5 weeks age, mice were injected subcutaneously with 3×10^6 DLD-1 or DLD-1 BRCA2-KO cells suspended in 100 μ L PBS. Tumor take rate was >80%. When tumors reached 100 mm³ geometric mean volume, the mice were injected with 3 mg/kg YU238259 or 3:1 DMSO:PBS vehicle (IP, 100 μ L total). Treatment was repeated 3x/week (Mon/Wed/Fri) until each tumor group had received 12 doses. Tumor growth was assessed by external caliper. Mice were euthanized when individual tumor volumes exceeded 1000 mm³.

Example 1: High-throughput screening reveals small molecules that are synthetically lethal to HDR-deficient cells.

In order to identify small molecules with synthetic lethality in the context of HDR defects, the screen made use of paired cell lines deficient and proficient in FANCD2 (PD20) and BRCA2 (PEO1/4) activity (Fig. 1A). Following optimization, Z' values were >0.5, indicating excellent discrimination between positive and negative controls. Screening compounds that demonstrated increased cytotoxicity in both FANCD2- and BRCA2-deficient cells relative to repair-proficient counterparts, as well as achieving a minimum cytotoxic effect, were considered "hits."

Initial screening of 15,040 molecules in the ChemBridge DIVERSet library identified a number of candidates, four of which showed synthetic lethality with FANCD2- and BRCA2-deficiency (Fig. 1B) and possessed a similar sulfonamide backbone (Fig. 1C). A highly active fifth compound, YU175534, was identified through subsequent screening of structurally homologous molecules across other libraries. Following multiple rounds of chemical synthesis and structure-activity relationship analysis, the derivative compound YU238259 was identified (Fig. 1D). YU238259 was selected for additional study.

Example 2: YU238259 inhibits homology-dependent DSB repair.

The toxicity of these novel sulfonamide compounds in cells with HDR defects, combined with low toxicity in repair-proficient cells, is strikingly similar to the effects of PARP inhibition. An in vitro assay of PARP enzymatic activity, however, demonstrated no decrease in PARP activity after treatment with an initial screening hit, YU128440 (Fig. 2A). Further, circular dichroism spectroscopy showed that YU128440 does not intercalate into DNA (Fig. 2B).

It is possible that inhibition of DSB repair pathways may underlie the activity

of these compounds. To investigate this possibility, the U2OS cell lines DR-GFP and EJ5-GFP, which contain integrated GFP genes engineered to report repair of DNA double-strand breaks via the HDR and NHEJ pathways, respectively, were used. Each reporter contains a restriction enzyme sequence that can be cleaved by introduction of an I-Sce I expression
5 plasmid. In each case, repair of the Sce-I-induced DSB via the respective pathway resulted in expression of full-length, active GFP (Fig. 2C). YU238259 was added to U2OS DR-GFP cells and to the U2OS EJ5-GFP cells 24 hours prior to DSB induction, and treatment was maintained until cell harvest for FACS analysis. YU238259-treated cells exhibited a significant, dose-dependent decrease in HDR efficiency, as quantified by percentage of cells
10 expressing GFP, but no reduction in NHEJ frequency (Fig. 2D). Without wishing to be limited by any theory, the slight upward trend in NHEJ activity seen with increasing doses of YU238259 may suggest a compensatory shift to NHEJ in the context of inhibition of HDR at an early step in the pathway. Taken together, the results indicate that the synthetic lethality of YU238259, YU175534 and related hits in HDR-deficient cells is unrelated to PARP
15 inhibition or DNA intercalation. Rather, cellular activity appears to result from further inhibition of the HDR pathway, leading to accumulation of unresolved DSBs.

Example 3: YU238259 exhibits synthetic lethality with loss of frequently mutated tumor suppressors.

20 Although initial screening was carried out for synthetic lethality in the context of BRCA2 or FANCD2 loss, the potent inhibition of HDR by YU238259 suggested that synthetic lethality might be observed for other DNA repair- or DNA damage response-defective cells. Indeed, in paired, isogenic cell lines deficient or proficient in BRCA2 (DLD-1), ATM (GM05849), and PTEN (U251), YU238259 was significantly more toxic to DNA
25 repair or DNA damage response-deficient cells than their repair-proficient counterparts (Figs. 3A-3C). The cytotoxicity of YU238259 is thus not cell line-specific, and synthetic lethality exists for a variety of cells with DNA repair or damage response pathway mutations.

It was also investigated whether siRNA-mediated knockdown of the repair factors ATR, ATRIP, and NBS1 would sensitize A549 cells to YU238259 treatment. The
30 overall toxicity of ATR loss precluded any determination of synthetic lethality in the case of ATR knockdown; however, siRNA against ATRIP and NBS1 rendered cells sensitive to YU238259 (Fig. 3D).

These compounds also showed synthetic lethality to primary human melanoma cells that are deficient in PTEN activity, as was observed for the human glioma

line U251, above. In the case of melanoma, however, this effect appeared to be dependent on AKT status (Fig. 3E). YU238259 demonstrated synthetic lethality in a PTEN-mutant primary human melanoma line, YURIF, in which there is minimal activation of the AKT pathway at baseline. In the PTEN-null YUGEN8 line, there is hyperactivation of the AKT pathway at baseline, as evidenced by elevated pAKT levels. YU238259 treatment alone showed little cytotoxicity in these cells, but there was a strong synergistic effect when combined with an AKT inhibitor, MK-2206 (Fig. 3E). The synthetic lethality of YU238259 in the setting of PTEN loss is thus applicable to human cancers that frequently exhibit this mutation.

Example 4: YU238259 sensitizes tumor cells to radiation therapy and DSB-inducing chemotherapy.

Inhibition of DNA repair pathways can potentiate the cytotoxicity of radiotherapy and chemotherapy. In certain embodiments, HDR inhibition by YU238259 would enable it to synergize with ionizing radiation and drugs that generate DSBs. The pretreatment of DLD-1 and DLD-1 BRCA2-KO cells with YU238259 enhanced the effectiveness of ionizing radiation or etoposide (Figs. 4A-4B and 4D-4E). In DLD-1 BRCA2-KO cells, YU238259 plus IR and YU238259 plus etoposide were mathematically synergistic at all dose combinations, using the method of Chou and Talalay (Chou & Talalay, 1981, FEBS 115(1):207-216). Interestingly, the combination of YU238259 with the PARP inhibitor, olaparib, was also synergistic in DLD-1 BRCA2-KO cells (Figs. 4C & 4F). This suggests that YU238259 is also able to potentiate the toxicity of endogenous lesions that subsequently progress into DSBs in the setting of BER inactivation through PARP inhibition.

Example 5: Growth of BRCA2-deficient tumor xenografts in nude mice is reduced by YU238259 treatment.

DLD-1 cells effectively form tumor xenografts in nude mice. To assess the in vivo synthetic lethality of YU238259, subcutaneous tumor xenografts were generated by subcutaneous injection of 3×10^6 DLD-1 or DLD-1 BRCA2-KO cells into the flanks of nude mice. The mice then received repeated doses of 3 mg/kg YU238259 or 5 mg/kg YU128440 by intraperitoneal injection. DLD-1 (BRCA2-proficient) tumor xenografts were not responsive to treatment, but DLD-1 BRCA2-KO xenografts demonstrated a delay in tumor growth and the mice showed an increase in overall survival after YU238259 or YU128440 treatment, relative to vehicle (Fig. 5). These data recapitulate the synthetic lethality of

YU238259 treatment in BRCA2-deficient cultured cells.

Example 6: The mechanism of action of YU238259 appears to involve a proximal step in DNA end processing and repair following DSB induction.

5 Divergence of the HDR and NHEJ pathways occurs relatively early in the DNA damage response. Given the loss of recombination in the cell-based assay, elements of damage response pathways were investigated in the context of YU238259 treatment. Using a neutral comet assay, a measure of the number of DSBs in individual cells, YU238259-treated A549 cells had significantly higher levels of DSBs 24 h after 10 Gy IR compared to DMSO-
10 treated controls (Fig. 6A), consistent with impaired resolution of DSBs owing to HDR inhibition. No significant increase in DSBs was seen with YU238259 treatment in the absence of IR, even at 24 h of treatment. Additionally, activation of the checkpoint kinase CHK1 by 5 Gy IR was inhibited by YU238259 but was not inhibited when induced by 10 J/m² UV exposure (Fig. 6B). However, there was no change in levels of RPA activation in
15 response to either treatment. Taken together, these results suggest a defect in signaling in response to DSBs, specifically, rather than other DNA lesions.

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety.

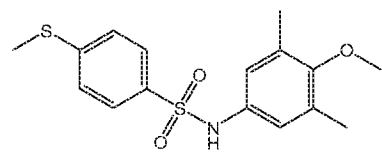
20 While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

CLAIMS

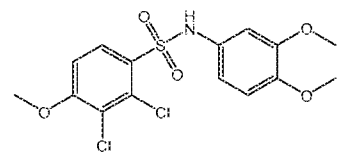
What is claimed:

1. A method of treating or preventing a DNA repair protein-deficient cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of at least one compound, or a salt or solvate thereof, selected from the group consisting of:

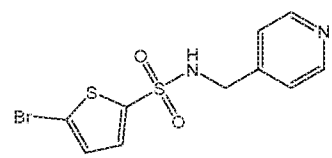
N-(4-methoxy-3,5-dimethyl phenyl)-4-(methylthio)benzenesulfonamide (YU126919)



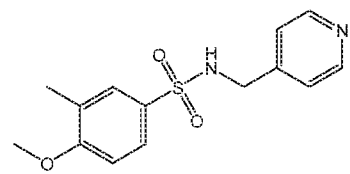
2,3-dichloro-N-(3,4-dimethoxy phenyl)-4-methoxybenzenesulfonamide (YU127190)



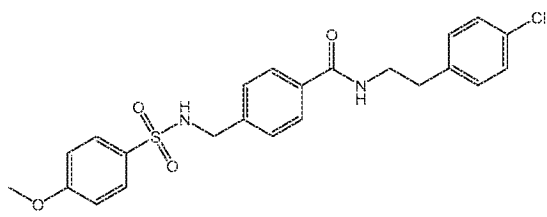
5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide (YU128355)



4-methoxy-3-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (YU128440)

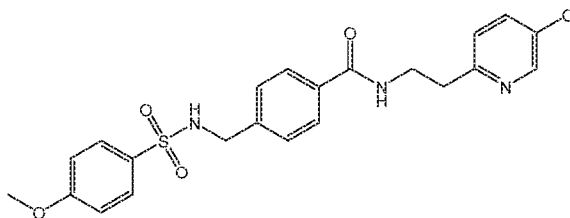


N-(4-chlorophenethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide (YU175534)



and,

N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl)benzamide (YU238259)



whereby the cancer is treated or prevented in the subject.

2. The method of claim 1, wherein the at least one compound inhibits DNA double strand break repair in the cancer.

3. The method of claim 2, wherein the at least one compound inhibits homology-dependent DNA repair in the cancer.

4. The method of claim 1, wherein the cancer is deficient in at least one protein selected from the group consisting of BRCA1, BRCA2, PTEN, ATM, PALB2, FANCD2, CHK2, RAD51 paralogs, MRE11, NBS1, RAD50, ATR, ATRIP, MEN1 and any other Fanconi pathway factors.

5. The method of claim 1, wherein the cancer is deficient in at least one selected from the group consisting of BRCA2 and PTEN.

6. The method of claim 1, wherein the subject is further administered at least one additional antitumor agent.

7. The method of claim 6, wherein the antitumor agent is at least one selected from the group consisting of topoisomerase inhibitors; alkylating agents; nitrosoureas; antimetabolites; antitumor antibiotics; antimicrotubule agents; hormonal agents; DNA strand break inducing agents; EGF receptor inhibitors and anti-EGF receptor antibodies; AKT inhibitors; mTOR inhibitors; CDK inhibitors; receptor tyrosine kinase (RTK) inhibitors; ribonucleotide reductase inhibitors; immune checkpoint inhibitors; and miscellaneous agents.

8. The method of claim 6, wherein administration of the at least one compound and at least one additional antitumor agent is synergistic.

9. The method of claim 6, wherein the at least one compound and at least one additional antitumor agent are co-administered to the subject.

10. The method of claim 9, wherein the at least one compound and at least one additional antitumor agent are coformulated.

11. The method of claim 1, wherein the subject is further administered radiation therapy.

12. The method of claim 11, wherein administration of the at least one compound and the radiation therapy is synergistic.

13. The method of claim 1, wherein the at least one compound is administered to the subject through a route selected from the group consisting of oral, transdermal, transmucosal, intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, pleural, peritoneal, subcutaneous, epidural, otic, intraocular, and topical.

14. The method of claim 1, wherein the cancer comprises at least one selected from the group consisting of breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, glioma, meningioma, glioblastoma multiforme, melanoma, lymphoma, leukemia, lung cancer, endometrial cancer, head and neck cancer, sarcoma, multiple myeloma and neuroblastoma.

15. The method of claim 1, wherein the cancer comprises at least one selected from the group consisting of breast cancer, ovarian cancer, melanoma, head and neck cancer, sarcoma, multiple myeloma and brain cancer.

16. The method of claim 1, wherein the cancer is deficient in PTEN activity and wherein the subject is further administered a therapeutically effective amount of an AKT inhibitor.

17. The method of claim 16, wherein the cancer comprises glioma or melanoma.

18. The method of claim 1, wherein the subject is a mammal.

19. The method of claim 18, wherein the mammal is a human.

20. A kit comprising at least one compound or a salt or solvate thereof, an applicator, and an instructional material for use thereof, wherein the instructional material comprises instructions for treating or preventing a DNA repair protein-deficient cancer in a subject in need thereof, wherein the at least one compound is selected from the group consisting of N-(4-methoxy-3,5-dimethyl phenyl)-4-(methylthio)benzenesulfonamide (YU126919); 2,3-dichloro-N-(3,4-dimethoxy phenyl)-4-methoxybenzenesulfonamide (YU127190); 5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide (YU128355); 4-methoxy-3-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (YU128440); and, N-(4-chlorophenethyl)-4-(((4-methoxyphenyl) sulfonamido)methyl)benzamide (YU175534); and, N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido)methyl) benzamide (YU238259).

21. The kit of claim 20, further comprising at least one additional antitumor agent.

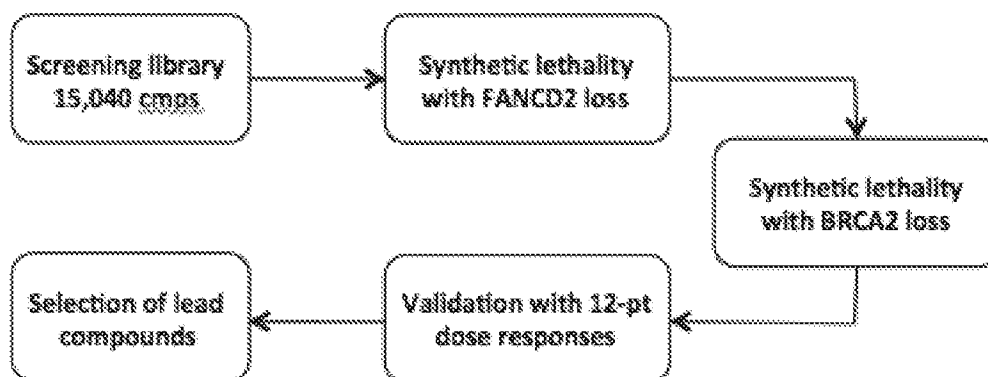
22. The kit of claim 21, wherein the at least one compound and at least one additional antitumor agent are coformulated.

23. A pharmaceutical composition comprising at least one compound, or a salt or solvate thereof, selected from the group consisting of N-(4-methoxy-3,5-dimethyl phenyl)-4-(methylthio)benzenesulfonamide (YU126919); 2,3-dichloro-N-(3,4-dimethoxy phenyl)-4-methoxybenzenesulfonamide (YU127190); 5-bromo-N-(pyridin-4-ylmethyl) thiophene-2-sulfonamide (YU128355); 4-methoxy-3-methyl-N-(pyridin-4-ylmethyl) benzenesulfonamide (YU128440); and, N-(4-chlorophenethyl)-4-(((4-methoxyphenyl) sulfonamido)methyl)benzamide (YU175534); and, N-(2-(5-chloropyridin-2-yl)ethyl)-4-(((4-methoxyphenyl)sulfonamido) methyl)benzamide (YU238259).

24. The pharmaceutical composition of claim 23, further comprising at least one additional antitumor agent, or a salt or solvate thereof.

25. The pharmaceutical composition of claim 24, wherein the at least one compound and at least one additional antitumor agent are coformulated in the same pharmaceutical formulation.

26. The pharmaceutical composition of claim 23, further comprising at least one AKT inhibitor, or a salt or solvate thereof.

Fig. 1AFig. 1B

	FANCD2 +/+	FANCD2 -/-	BRCA2 +/+	BRCA2 -/-
YU126919	inactive	16.21	8.94	5.56
YU127190	inactive	inactive	12.42	7.92
YU128355	13.3	4.53	1.93	0.84
YU128440	9.59	4.68	2.51	0.97

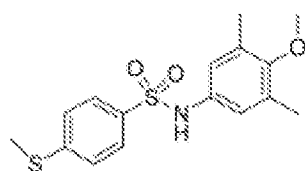
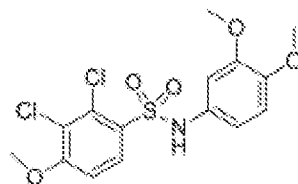
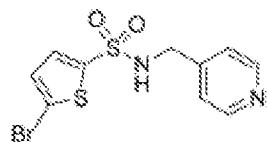
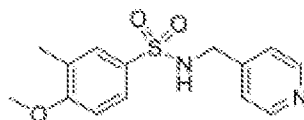
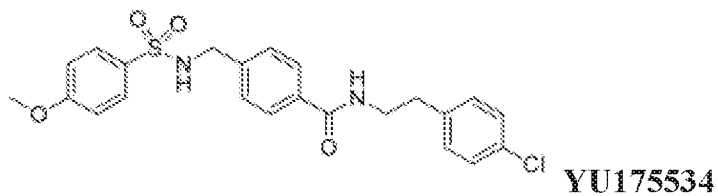
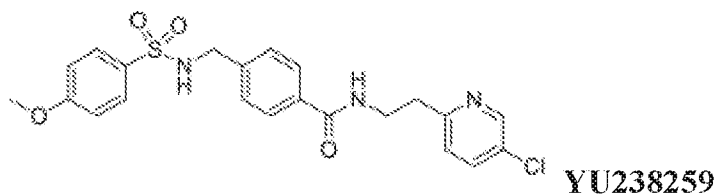
Fig. 1C**YU126919****YU127190****YU128355****YU128440**Fig. 1D**YU175534****YU238259**

Fig. 2A

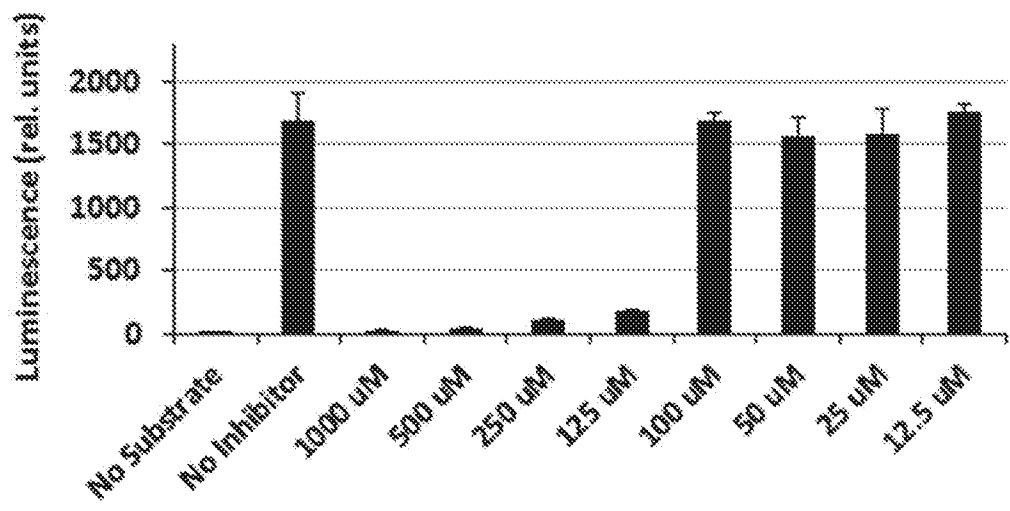


Fig. 2B

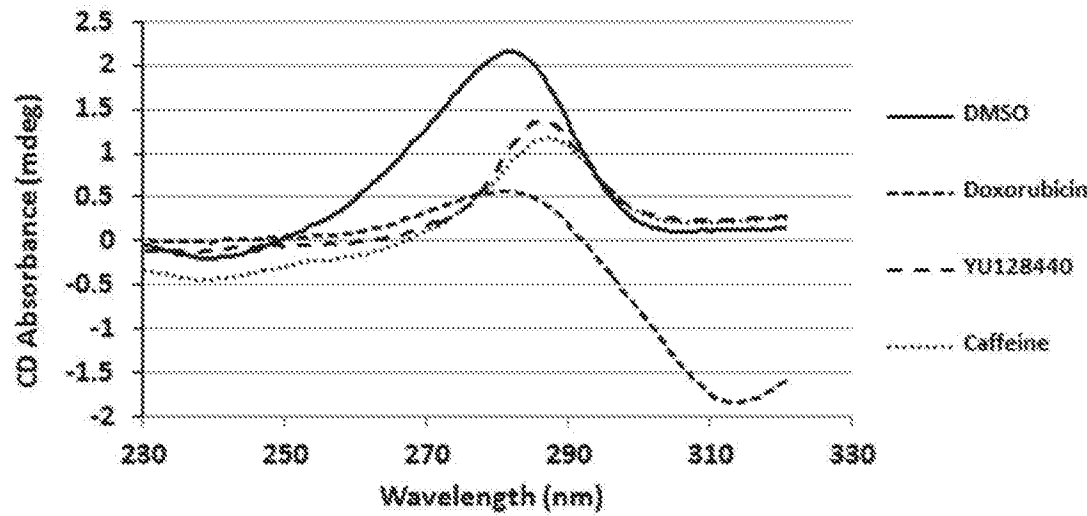


Fig. 2C

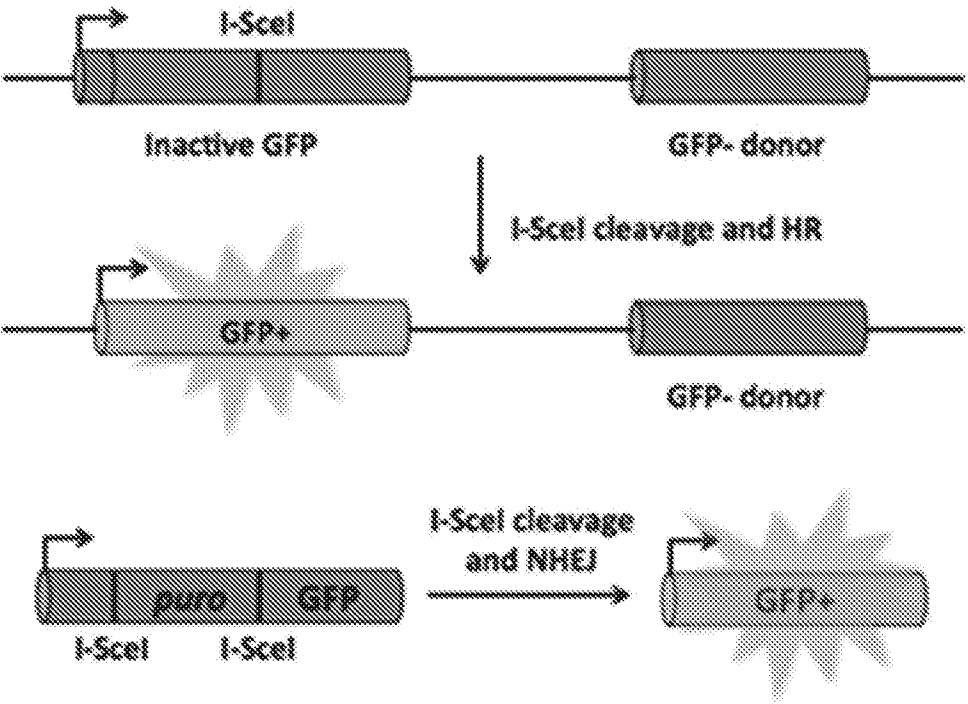


Fig. 2D

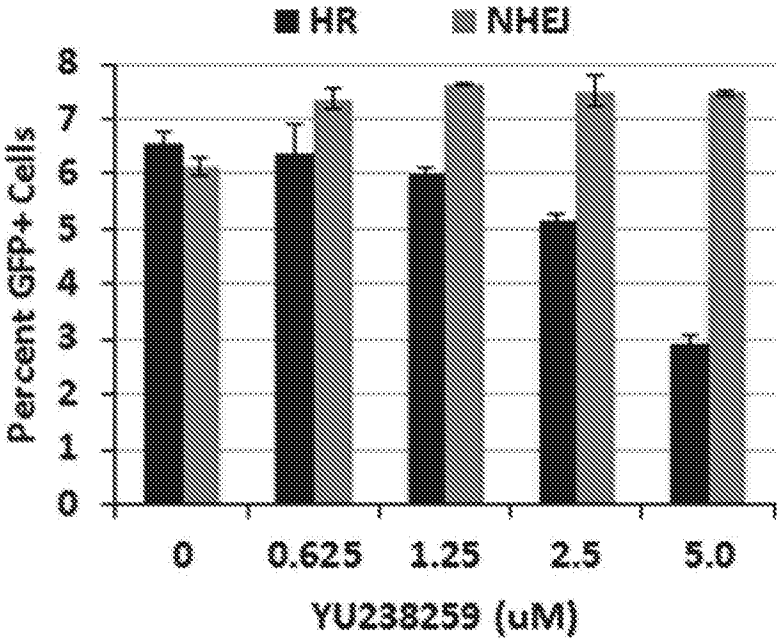


Fig. 3A

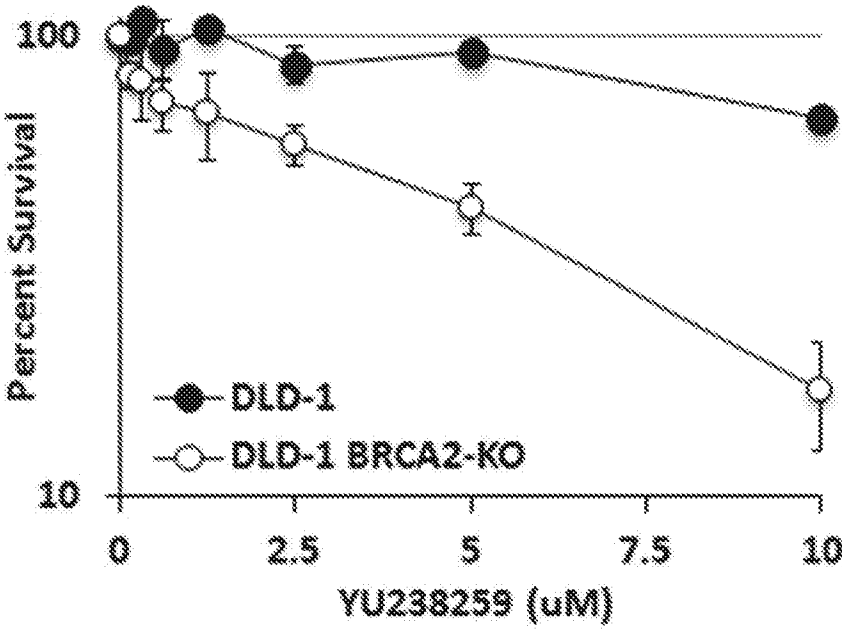


Fig. 3B

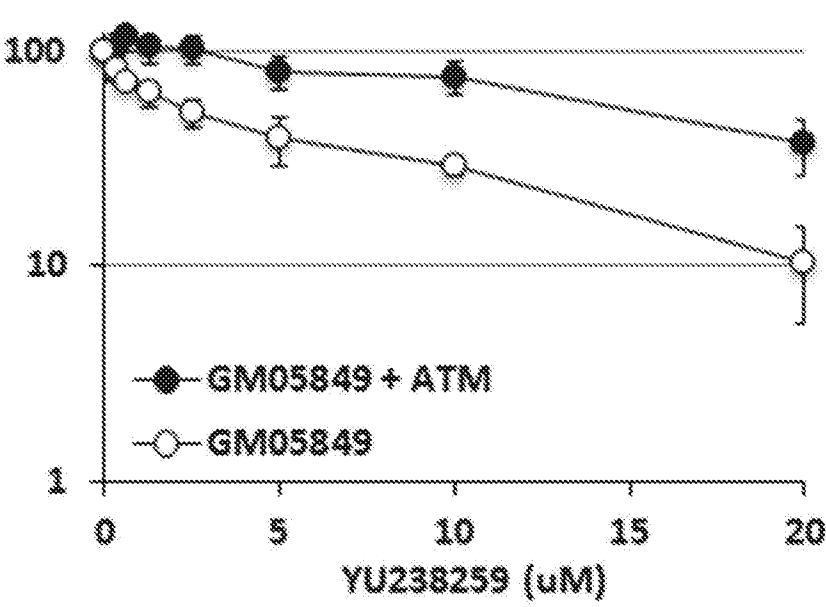


Fig. 3C

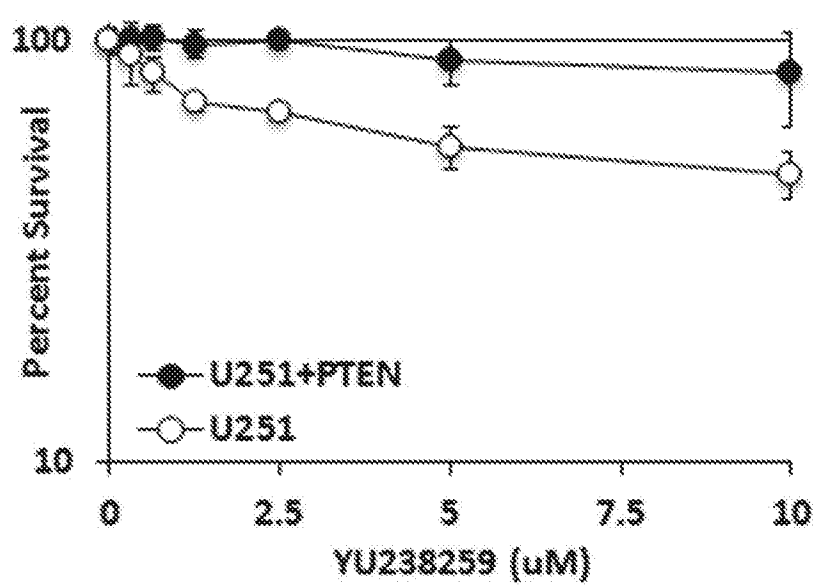


Fig. 3D

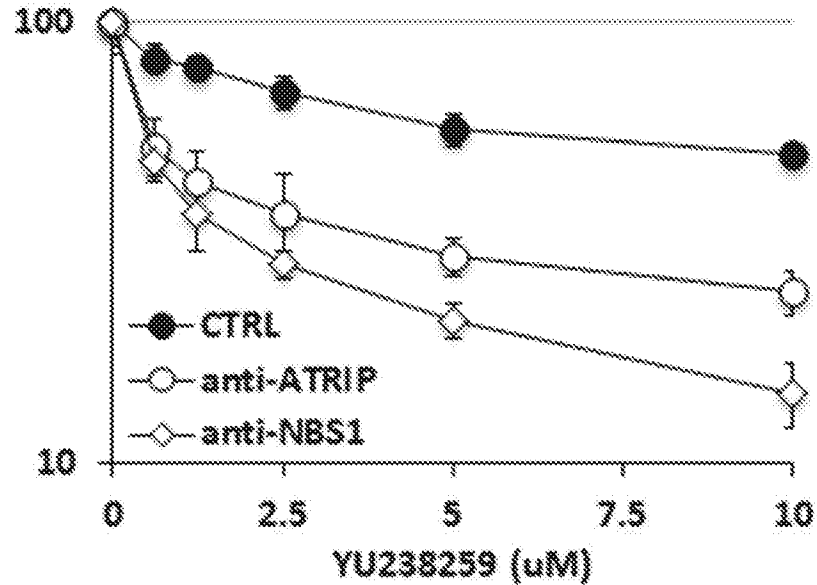


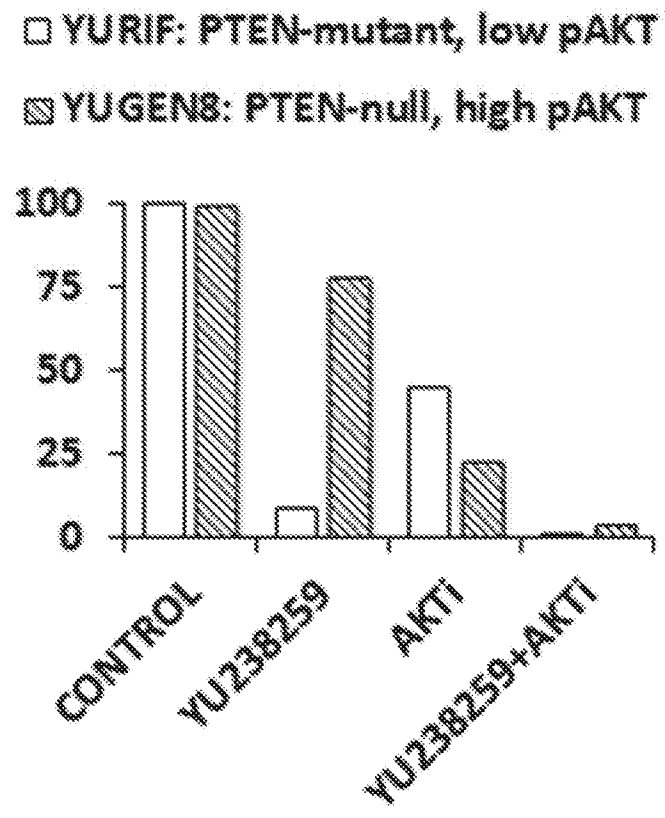
Fig. 3E

Fig. 4A

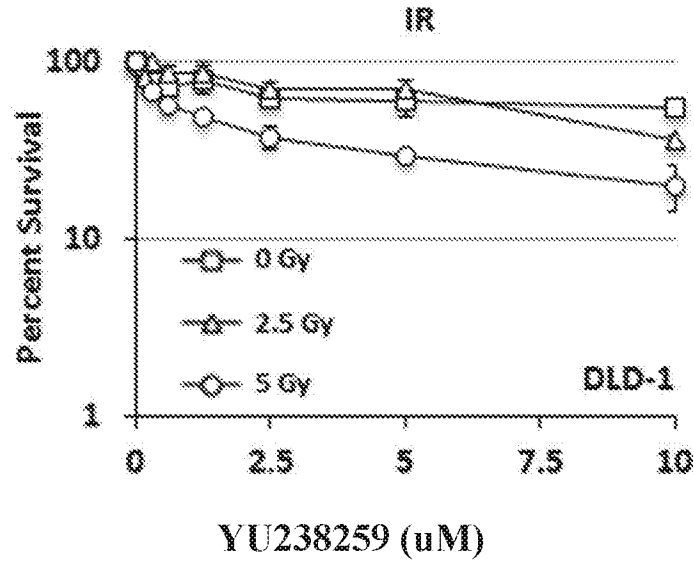


Fig. 4B

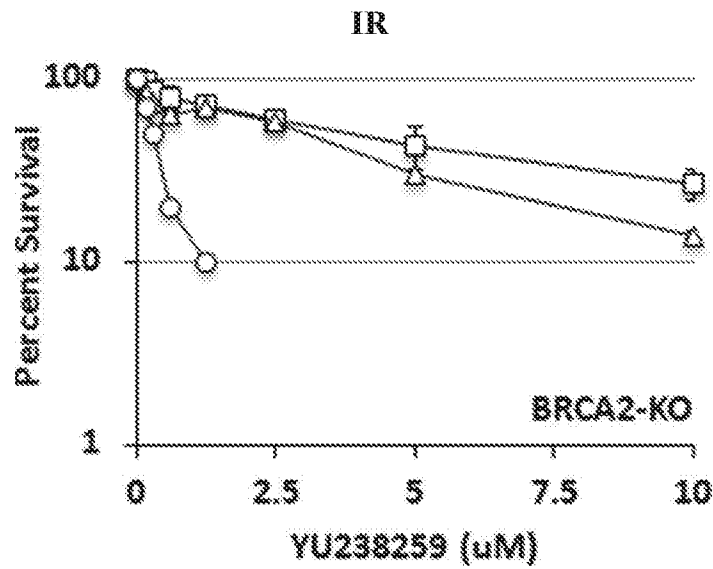


Fig. 4C

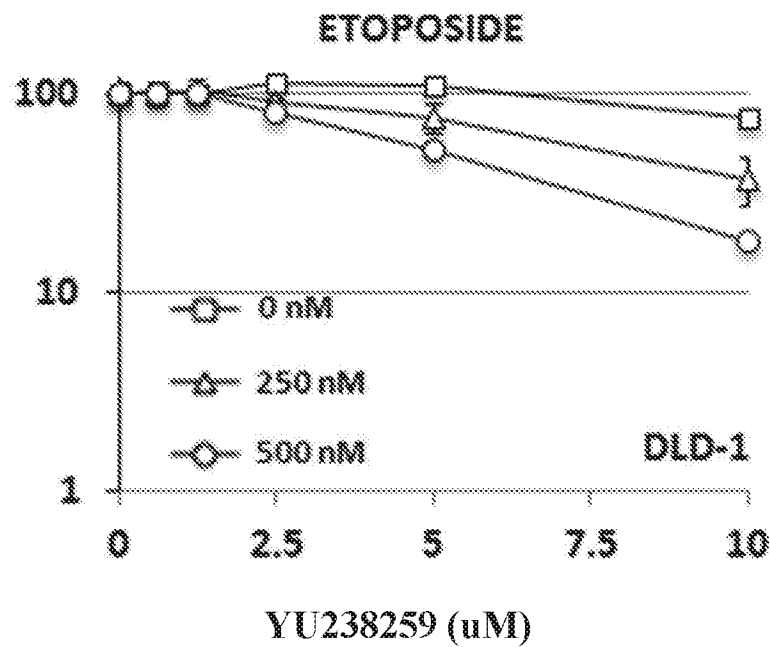


Fig. 4D

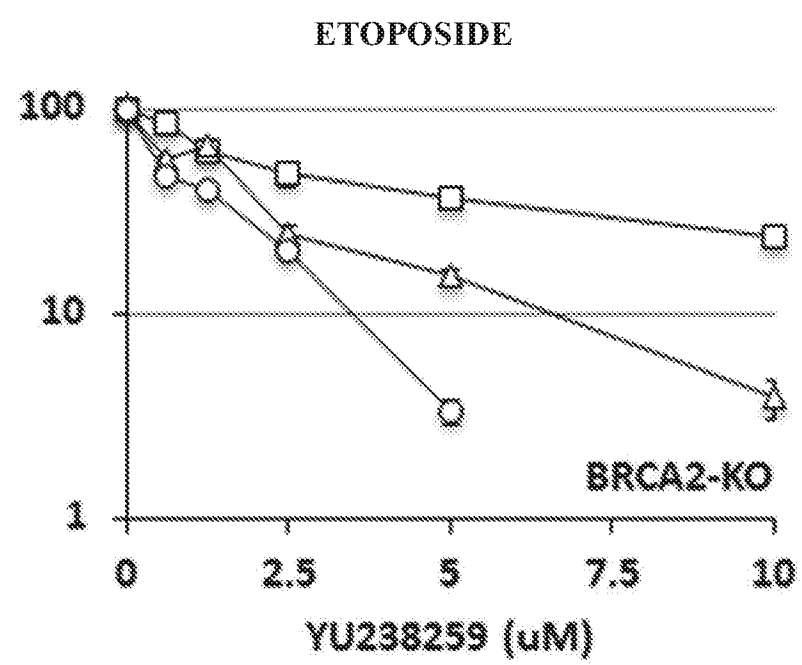


Fig. 4E

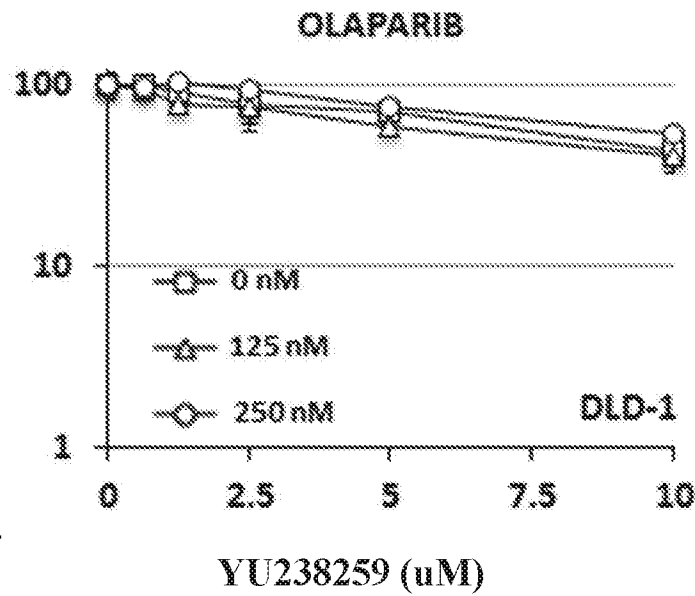


Fig. 4F

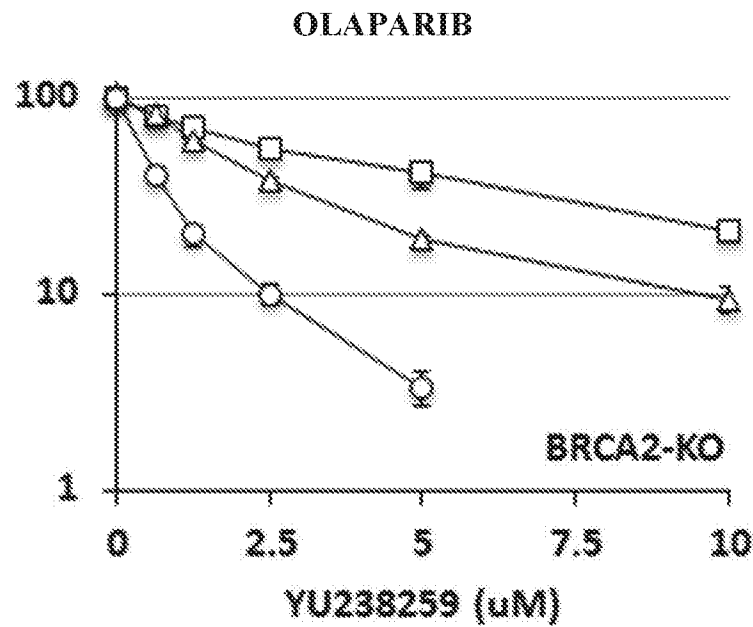


Fig. 5A

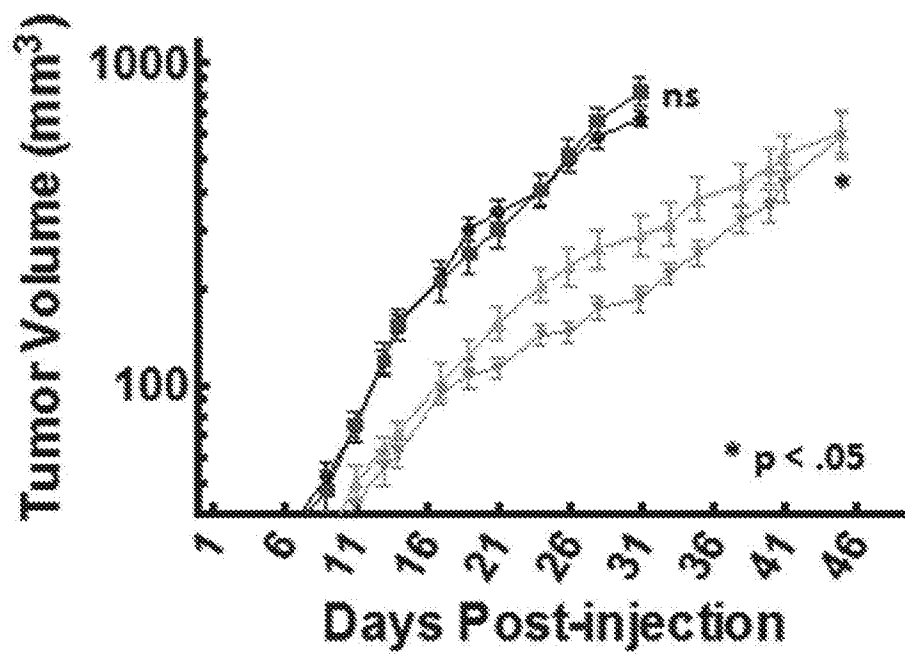


Fig. 5B

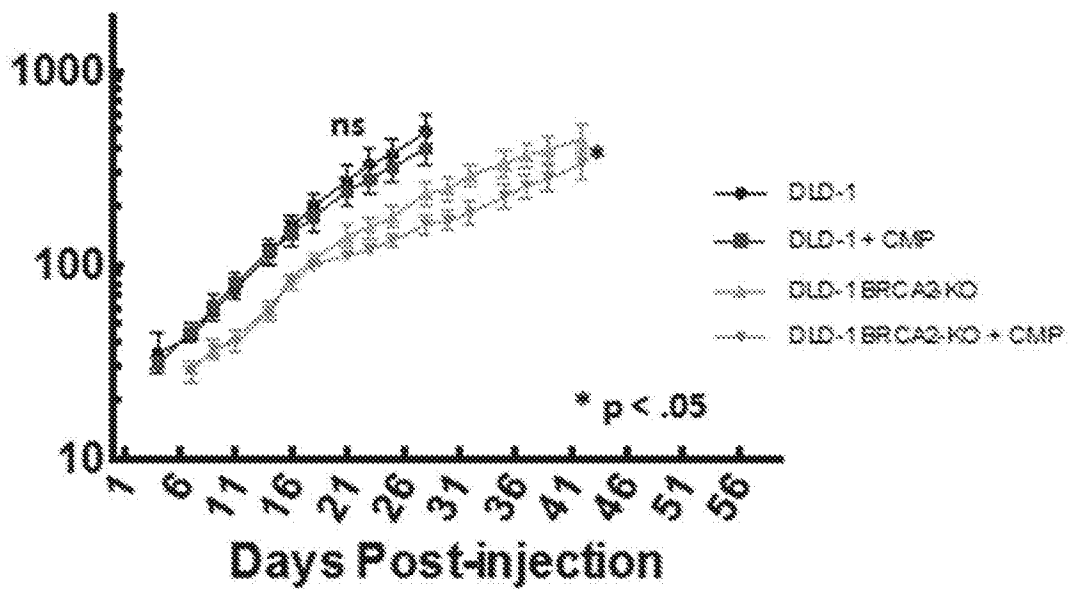


Fig. 5C

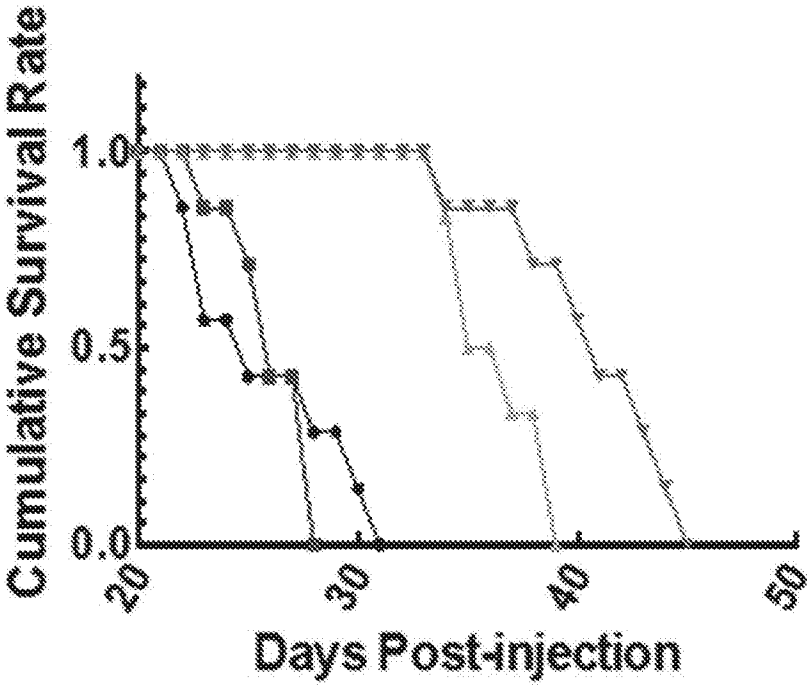


Fig. 5D

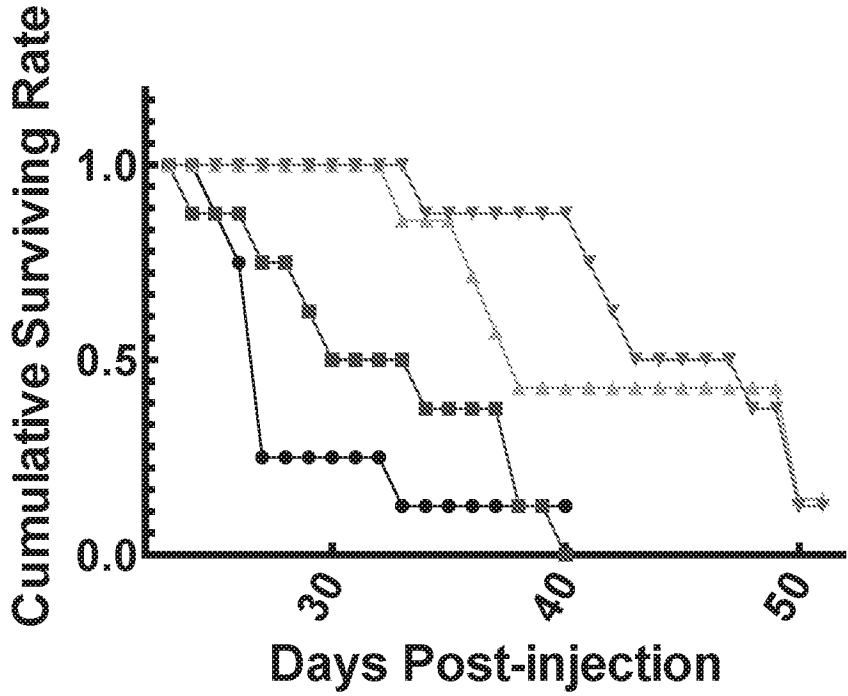


Fig. 6A

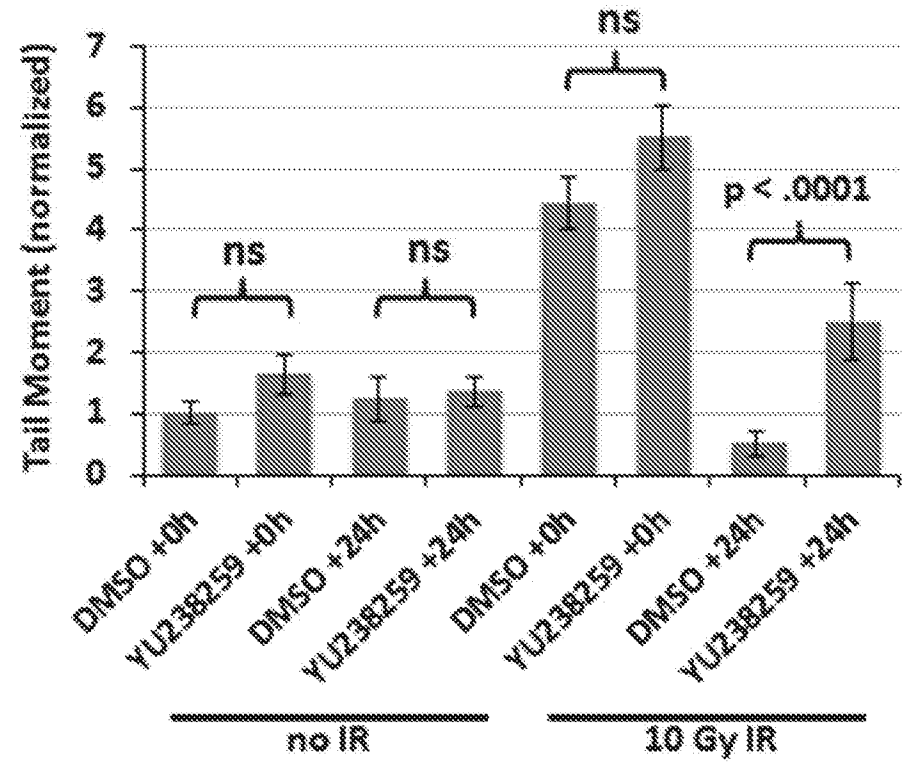
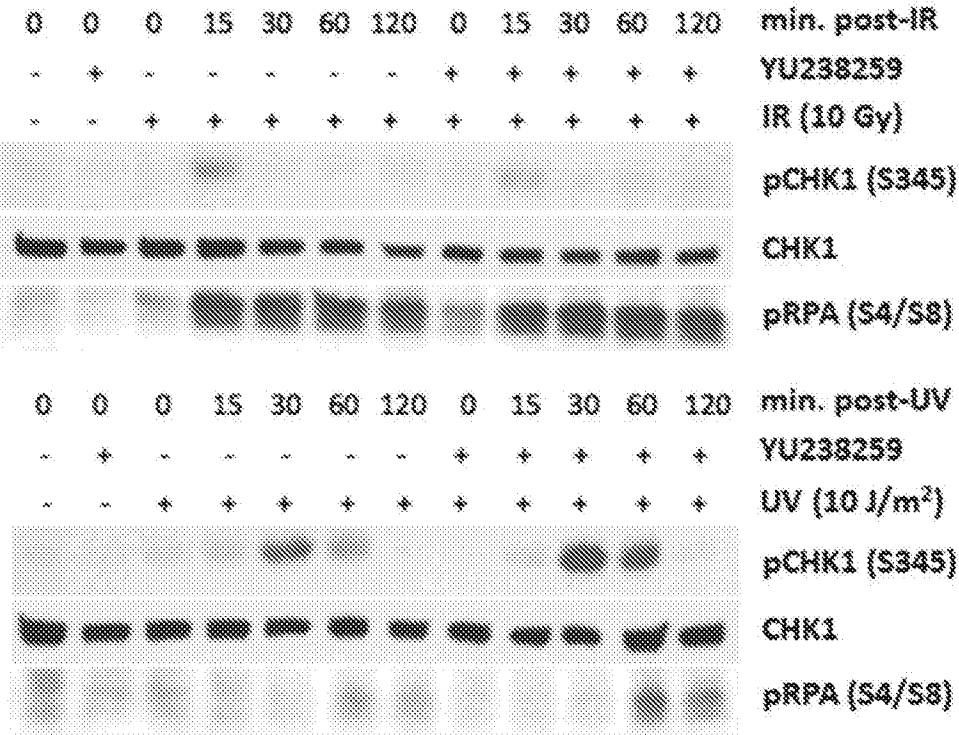


Fig.6B



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/12460

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 35/00; C07C 311/21, 311/29 (2016.01)

CPC - C07C 311/44; C07D 213/16, 333/12

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)

IPC(8): A61P 35/00; C07C 311/21, 311/29 (2016.01)

CPC: C07C 311/44; C07D 213/16, 333/12

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

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

PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google Scholar; IP.com; SureChEMBL; KEYWORDS: cancer*, benzenesulfonamide, combin* anti cancer, cancer* deficient*, BRCA2 deficient*, double strand break repair, treat* cancer*, topoisomerase, alkylat* agent*, breast cancer*, YU126919, YU127190, YU128355

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2004/005278 A1 (CYCLACEL LIMITED) 15 January 2004; page 4, lines 1-25; page 5, lines 1-24; page 6, lines 4-6, 21-23; page 26, lines 26-28; page 27, lines 23-24; page 49, line 17; page 50, lines 1-5	23-25 --- 26
Y	US 2014/0357618 A1 (MERCK SHARP & DOHME CORP.) 04 December 2014; abstract; paragraphs [0426], [0486], [0564]	26
A	US 2012/0135983 A1 (ASHWORTH, A et al.) 31 May 2012; paragraphs [0001], [0011], [0016], [0060], [0067]	1-22
A	US 2013/0184342 A1 (THE JACKSON LABORATORY) 18 July 2013; paragraphs [0124], [0257], [0320]	1-22
A	US 2009/0149397 A1 (OSSOVSKAYA, V et al.) 11 June 2009; paragraphs [0007], [0020], [0024], [0070], [0074]	1-22
P,Y	STACHELEK, GC et al., YU238259 Is a Novel Inhibitor of Homology-Dependent DNA Repair That Exhibits Synthetic Lethality and Radiosensitization in Repair-Deficient Tumors, Molecular Cancer Research Vol. 13 (10), pages 1389-97, Published Online 26 June 2015; <DOI: 10.1158/1541-7786.MCR-15-0036>; entire document	1-26

☐ 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

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"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

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"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

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Date of the actual completion of the international search

29 February 2016 (29.02.2016)

Date of mailing of the international search report

21 MAR 2016

Name and mailing address of the ISA/

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