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(54) **Title**: USE OF DIANHYDROGALACTITOL AND ANALOGS OR DERIVATIVES THEREOF TO TREAT NON-SMALL-CELL CARCINOMA OF THE LUNG AND OVARIAN CANCER

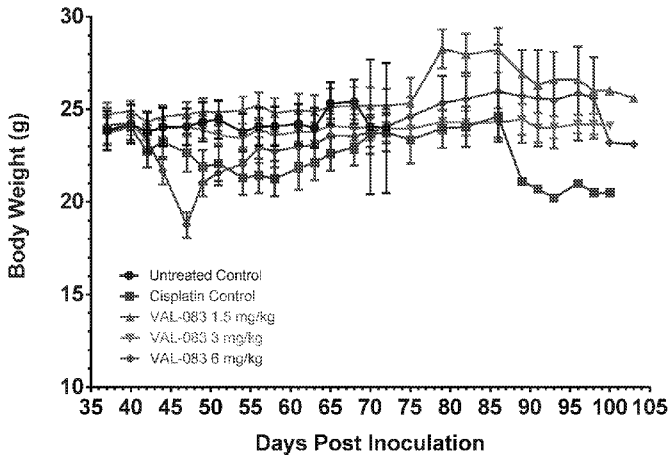


Figure 1

(57) **Abstract**: The use of dianhydrogalactitol provides a novel therapeutic modality for the treatment of non-small-cell lung carcinoma (NSCLC) and ovarian cancer. Dianhydrogalactitol acts as an alkylating agent on DNA that creates N^7 methylation. Dianhydrogalactitol is effective in suppressing the growth of cancer stem cells and is active against tumors that are refractory to temozolomide, cisplatin, and thymidine kinase inhibitors; the drug acts independently of the MGMT repair mechanism. Dianhydrogalactitol can be used together with other anti-neoplastic agents and can possess additive or super-additive effects.

WO 2015/154064 A2

USE OF DIANHYDROGALACTITOL AND ANALOGS OR DERIVATIVES THEREOF TO TREAT NON-SMALL-CELL CARCINOMA OF THE LUNG AND OVARIAN CANCER

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of United States Provisional Patent Application Serial No. 61/975,587 by J.A. Bacha et al., filed April 4, 2014 and entitled "Use of Dianhydrogalactitol and Analogs and Derivatives Thereof to Treat Non-Small-Cell Carcinoma of the Lung" and United States Provisional Patent Application Serial No. 62/062,246 by J. Bacha et al., filed October 10, 2014 and entitled "Use of Dianhydrogalactitol and Analogs and Derivatives Thereof to Treat Non-Small-Cell Carcinoma of the Lung." The contents of both of these United States provisional patent applications are incorporated herein in their entirety by this reference.

FIELD OF THE INVENTION

[0002] The present invention relates to the general field of hyperproliferative diseases including oncology with a focus on novel methods and compositions for the improved utility of chemical agents, compounds, and dosage forms previously limited by suboptimal human therapeutic performance including substituted hexitols such as dianhydrogalactitol and diacetyldianhydrogalactitol, as well as other classes of chemical agents. In particular, the present invention relates to the treatment of non-small-cell carcinoma of the lung with dianhydrogalactitol, diacetyldianhydrogalactitol, or derivatives or analogs thereof.

BACKGROUND OF THE INVENTION

[0003] The search for and identification of cures for many life-threatening diseases that plague humans still remains an empirical and sometimes serendipitous process. While many advances have been made from basic scientific research to improvements in practical patient management, there still remains tremendous frustration in the rational and successful discovery of useful therapies particularly for

life-threatening diseases such as cancer, inflammatory conditions, infection, and other conditions.

[0004] Since the "War on Cancer" began in the early 1970's by the United States National Cancer Institute (NCI) of the National Institutes of Health (NIH), a wide variety of strategies and programs have been created and implemented to prevent, diagnose, treat and cure cancer. One of the oldest and arguably most successful programs has been the synthesis and screening of small chemical entities (<1500 MW) for biological activity against cancer. This program was organized to improve and streamline the progression of events from chemical synthesis and biological screening to preclinical studies for the logical progression into human clinical trials with the hope of finding cures for the many types of life-threatening malignant tumors. The synthesis and screening of hundreds of thousands of chemical compounds from academic and industrial sources, in addition to the screening of natural products and extracts from prokaryotes, invertebrate animals, plant collections, and other sources from all over the world has been and continues to be a major approach for the identification of novel lead structures as potential new and useful medicines. This is in addition to other programs including biotherapeutics designed to stimulate the human immune system with vaccines, therapeutic antibodies, cytokines, lymphokines, inhibitors of tumor blood vessel development (angiogenesis) or gene and antisense therapies to alter the genetic make-up of cancer cells, and other biological response modifiers.

[0005] The work supported by the NCI, other governmental agencies both domestic and foreign in academic or industrial research and development laboratories has resulted in an extraordinary body of biological, chemical and clinical information. In addition, large chemical libraries have been created, as well as highly characterized *in vitro* and *in vivo* biological screening systems that have been successfully used. However, from the tens of billions of dollars spent over the past thirty years supporting these programs both preclinically and clinically, only a small number of compounds have been identified or discovered that have resulted in the successful development of useful therapeutic products. Nevertheless, the biological systems both *in vitro* and *in vivo* and the "decision trees" used to warrant further animal studies leading to clinical studies have been validated. These programs, biological models, clinical trial protocols,

and other information developed by this work remain critical for the discovery and development of any new therapeutic agent.

[0006] Unfortunately, many of the compounds that have successfully met the preclinical testing and federal regulatory requirements for clinical evaluation were either unsuccessful or disappointing in human clinical trials. Many compounds were found to have untoward or idiosyncratic side-effects that were discovered during human clinical Phase I dose-escalation studies used to determine the maximum tolerated dose (MTD) and side-effect profile. In some cases, these toxicities or the magnitude of their toxicity were not identified or predicted in preclinical toxicology studies. In other cases, chemical agents where *in vitro* and *in vivo* studies suggested a potentially unique activity against a particular tumor type, molecular target or biological pathway were not successful in human Phase II clinical trials where specific examination of particular cancer indications/types were evaluated in government sanctioned (e.g., U.S. FDA), IRB approved clinical trials. In addition, there are those cases where potential new agents were evaluated in randomized Phase III clinical trials where a significant clinical benefit could not be demonstrated; such cases have also been the cause of great frustration and disappointment. Finally, a number of compounds have reached commercialization but their ultimate clinical utility has been limited by poor efficacy as monotherapy (<25% response rates) and untoward dose-limiting side-effects (Grade III and IV) (e.g., myelosuppression, neurotoxicity, cardiotoxicity, gastrointestinal toxicities, or other significant side effects).

[0007] In many cases, after the great time and expense of developing and moving an investigational compound into human clinical trials and where clinical failure has occurred, the tendency has been to return to the laboratory to create a better analog, look for agents with different structures but potentially related mechanisms of action, or try other modifications of the drug. In some cases, efforts have been made to try additional Phase I or II clinical trials in an attempt to make some improvement with the side-effect profile or therapeutic effect in selected patients or cancer indications. In many of those cases, the results did not realize a significant enough improvement to warrant further clinical development toward product registration. Even for commercialized products, their ultimate use is still limited by suboptimal performance.

[0008] With so few therapeutics approved for cancer patients and the realization that cancer is a collection of diseases with a multitude of etiologies and that a patient's response and survival from therapeutic intervention is complex with many factors playing a role in the success or failure of treatment including disease indication, stage of invasion and metastatic spread, patient gender, age, health conditions, previous therapies or other illnesses, genetic markers that can either promote or retard therapeutic efficacy, and other factors, the opportunity for cures in the near term remains elusive. Moreover, the incidence of cancer continues to rise with an approximate 4% increase predicted for 2003 in the United States by the American Cancer Society such that over 1.3 million new cancer cases are estimated. In addition, with advances in diagnosis such as mammography for breast cancer and PSA tests for prostate cancer, more patients are being diagnosed at a younger age. For difficult to treat cancers, a patient's treatment options are often exhausted quickly resulting in a desperate need for additional treatment regimens. Even for the most limited of patient populations, any additional treatment opportunities would be of considerable value. This invention focuses on inventive compositions and methods for improving the therapeutic benefit of suboptimally administered chemical compounds including substituted hexitols such as dianhydrogalactitol.

[0009] Non-small-cell lung carcinoma (NSCLC) includes several types of lung cancer, including squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, as well as other types of lung cancer. Although smoking is apparently the most frequent cause of squamous cell carcinoma, when lung cancer occurs in patients without any history of prior tobacco smoking, it is frequently adenocarcinoma. In many cases, NSCLC is refractory to chemotherapy, so surgical resection of the tumor mass is typically the treatment of choice, particularly if the malignancy is diagnosed early. However, chemotherapy and radiation therapy are frequently attempted, particularly if the diagnosis cannot be made at an early stage of the malignancy. Other treatments include radiofrequency ablation and chemoembolization. A wide variety of chemotherapeutic treatments has been tried for advanced or metastatic NSCLC. Some patients with particular mutations in the *EGFR* gene respond to EGFR tyrosine kinase inhibitors such as gefitinib (M.G. Kris, "How Today's Developments in the Treatment of

Non-Small Cell Lung Cancer Will Change Tomorrow's Standards of Care," Oncologist 10 (Suppl. 2): 23-29 (2005), incorporated herein by this reference). Cisplatin has frequently been used as ancillary therapy together with surgery. Erlotinib, pemetrexed, About 7% of NSCLC have EML4-ALK translocations, and such patients may benefit from ALK inhibitors such as crizotinib. Other therapies, including the vaccine TG4010, motesanib diphosphate, tivantinib, belotecan, eribulin mesylate, ramucirumab, necitumumab, the vaccine GSK1572932A, custirsen sodium, the liposome-based vaccine BLP25, nivolumab, EMD531444, dacomitinib, and genetespib, are being evaluated, particularly for advanced or metastatic NSCLC.

[0010] However, there is still a need for effective therapies against NSCLC, especially against advanced or metastatic NSCLC. Preferably, such therapies should be well-tolerated and with side effects, if any, that could be easily controlled. Also, preferably, such therapies should be compatible with other chemotherapeutic approaches and with surgery or radiation. Additionally, and preferably, such therapies should be able to exert a synergistic effect on other treatment modalities.

SUMMARY OF THE INVENTION

[0011] The use of a substituted hexitol derivative to treat non-small-cell lung carcinoma (NSCLC) provides an improved therapy for NSCLC and ovarian cancer that yields increased survival and is substantially free of side effects. In general, the substituted hexitols usable in methods and compositions according to the present invention include galactitols, substituted galacitols, dulcitols, and substituted dulcitols. Typically, the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol. A particularly preferred substituted hexitol derivative is dianhydrogalactitol (DAG). The substituted hexitol derivative can be employed together with other therapeutic modalities for these malignancies. Dianhydrogalactitol is particularly suited for the treatment of these malignancies because it can suppress the growth of cancer stem cells (CSC), and because it is resistant to drug inactivation by O^6-methylguanine-DNA methyltransferase (MGMT). The substituted hexitol derivative

yields increased response rates and improved quality of life for patients with NSCLC and ovarian cancer.

[0012] Dianhydrogalactitol is a novel alkylating agent that creates N^7-methylation in DNA. Specifically, the principal mechanism of action of dianhydrogalactitol is attributed to bi-functional N^7 DNA alkylation, via actual or derived epoxide groups, which cross-links across DNA strands.

[0013] Accordingly, one aspect of the present invention is a method to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of NSCLC or ovarian cancer comprising the steps of:

(1) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the administration of the substituted hexitol derivative for treatment of NSCLC or ovarian cancer; and

(2) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the substituted hexitol derivative for treatment of NSCLC or ovarian cancer.

[0014] Typically, the factor or parameter is selected from the group consisting of:

(1) dose modification;
(2) route of administration;
(3) schedule of administration;
(4) indications for use;
(5) selection of disease stage;
(6) other indications;
(7) patient selection;
(8) patient/disease phenotype;
(9) patient/disease genotype;
(10) pre/post-treatment preparation;
(11) toxicity management;
(12) pharmacokinetic/pharmacodynamic monitoring;
(13) drug combinations;
(14) chemosensitization;
(15) chemopotentiation;

(16) post-treatment patient management;
(17) alternative medicine/therapeutic support;
(18) bulk drug product improvements;
(19) diluent systems;
(20) solvent systems;
(21) excipients;
(22) dosage forms;
(23) dosage kits and packaging;
(24) drug delivery systems;
(25) drug conjugate forms;
(26) compound analogs;
(27) prodrugs;
(28) multiple drug systems;
(29) biotherapeutic enhancement;
(30) biotherapeutic resistance modulation;
(31) radiation therapy enhancement;
(32) novel mechanisms of action;
(33) selective target cell population therapeutics;
(34) use with ionizing radiation;
(35) use with an agent that counteracts myelosuppression; and
(36) use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier to treat brain metastases of NSCLC or ovarian cancer.

[0015] As detailed above, typically, the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol. Preferably, the substituted hexitol derivative is dianhydrogalactitol.

[0016] Another aspect of the present invention is a composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy

employing a substituted hexitol derivative for the treatment of NSCLC or ovarian cancer comprising an alternative selected from the group consisting of:

(i) a therapeutically effective quantity of a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative, wherein the modified substituted hexitol derivative or the derivative, analog or prodrug of the substituted hexitol derivative or modified substituted hexitol derivative possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC as compared with an unmodified substituted hexitol derivative;

(ii) a composition comprising:

(a) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative, or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative; and

(b) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, drug delivery system, or agent to counteract myelosuppression, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC as compared with an unmodified substituted hexitol derivative;

(iii) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is incorporated into a dosage form, wherein the substituted hexitol derivative, the modified substituted hexitol derivative or the derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC as compared with an unmodified substituted hexitol derivative;

(iv) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is incorporated into a dosage kit and packaging, wherein the substituted hexitol derivative,

the modified substituted hexitol derivative or the derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative incorporated into the dosage kit and packaging possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC as compared with an unmodified substituted hexitol derivative; and

(v) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is subjected to a bulk drug product improvement, wherein substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative subjected to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC as compared with an unmodified substituted hexitol derivative.

[0017] As detailed above, typically the unmodified substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol. Preferably, the unmodified substituted hexitol derivative is dianhydrogalactitol.

[0018] Another aspect of the present invention is a method of treating NSCLC comprising the step of administering a therapeutically effective quantity of a substituted hexitol derivative to a patient suffering from the malignancy. As detailed above, the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol. Preferably, the substituted hexitol derivative is dianhydrogalactitol. The method can be used to treat patients who have developed resistance to tyrosine kinase inhibitors (TKI) or platinum-based chemotherapeutic agents such as cisplatin. The method can also be used together with TKI or platinum-based chemotherapeutic agents. Suitable platinum-based therapeutic chemotherapeutic agents include, but are not limited to, cisplatin and oxaliplatin.

[0019] Yet another aspect of the invention is a method of treating ovarian cancer comprising the step of administering a therapeutically effective quantity of a substituted hexitol derivative to a patient suffering from ovarian cancer. Suitable substituted hexitol derivatives are as described above; a particularly preferred substituted hexitol derivative is dianhydrogalactitol. In one alternative, the ovarian cancer is a cisplatin-resistant wild-type p53 cancer

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The following invention will become better understood with reference to the specification, appended claims, and accompanying drawings, where:

[0021] Figure 1 is a graph that shows body weight of female Rag2 mice after subcutaneous inoculation with 5 million A549 cells. Body weight is shown on the y-axis versus days post-inoculation on the x-axis for the results of the Example. In Figures 1-2 of the Example, • is the untreated control; ■ is the cisplatin control; ▲ is dianhydrogalactitol at 1.5 mg/kg; ▲ is dianhydrogalactitol at 3.0 mg/kg; and ♦ is dianhydrogalactitol at 6.0 mg/kg.

[0022] Figure 2 is a graph that shows the tumor volume (means ± S.E.M.) for the A549 tumor-bearing female Rag2 mice with tumor volume on the y axis versus days post-inoculation on the x-axis for the results of the Example. The top panel of Figure 2 represents all mice for the complete duration of the study. The bottom panel of Figure 2 represents all mice until day 70 (last day for untreated control group).

[0023] Figure 3 is a Kaplan-Meier survival plot in an in vivo model of A549 (TKI-sensitive) cells in female Rag2 mice comparing the effect of cisplatin at 5 mg/kg and dianhydrogalactitol at 1.5 mg/kg and 3.0 mg/kg for A549 (TKI-sensitive) cells.

[0024] Figure 4 is a Kaplan-Meier survival plot in an in vivo model of H1975 (TKI-resistant) cells in female Rag2 mice comparing the effect of cisplatin at 5 mg/kg and dianhydrogalactitol at 2 mg/kg, 3 mg/kg, and 4 mg/kg for H1975 (TKI-resistant) cells.

[0025] Figure 5 is a graph showing the effect of dianhydrogalactitol alone or with cisplatin (Figure 5A) or oxaliplatin (Figure 5B) on A549 (TKI-sensitive) cells *in vitro*. Data are shown as mean ± SE.

[0026] Figure 6 is a graph showing the effect of dianhydrogalactitol alone or with cisplatin (Figure 6A) or oxaliplatin (Figure 6B) on H1975 (TKI-resistant) cells *in vitro*. Data are shown as mean ± SE.

[0027] Figure 7 is a graph showing a dose-response curve in an ovarian tumor cell line panel treated with dianhydrogalactitol *in vitro*. The ovarian tumor panel lines are as follows: • is A2780; ■ is 2780-CP16; ▲ is OVCAR-10; ▼ is HEY; and ♦ is OVCA-433. Dose-reponse curves were undertaken using a 5-day MTT assay to determine cell viability. The A2780 represents a cisplatin-sensitive model, whereas the other four cell lines are cisplatin-resistant.

[0028] Figure 8 is a graph showing the *in vitro* cytotoxicity of dianhydrogalactitol ("DAG"), cisplatin ("cis-Pt") and oxaliplatin ("Oxali-Pt") in a wild-type p53 human ovarian tumor panel. The relative activity (IC50) of dianhydrogalactitol, cisplatin, and oxaliplatin against wild-type p53 ovarian tumor cells is shown.

[0029] Figure 9 is a graph showing the resistance factors of dianhydrogalactitol and the platinum drugs cisplatin and oxaliplatin in a wild-type p53 human ovarian tumor panel *in vitro*; the resistance factors are shown versus A2780. The activity of dianhydrogalactitol and the platinum drugs was normalized relative to the sensitive A2780 model. The graph indicates that the resistant tumor models are 10- to 30-fold resistant to cisplatin, 2- to 5-fold resistant to oxaliplatin, and 4- to 7-fold resistant to dianhydrogalactitol. Thus, cisplatin-resistant wild-type p53 ovarian tumor models demonstrate only partial cross-resistance to oxaliplatin and dianhydrogalactitol.

[0030] Figure 10 is a graph showing the cytotoxicity of cisplatin and relative resistance in a human NSCLC tumor panel *in vitro*. The cell lines used are H460, A549, H838, and H226, which have a wild-type p53; H1975, SkLU1, H2122, and H157, which have a mutated p53; and H1229, which has a null p53.

[0031] Figure 11 is a graph showing the cytotoxicity of oxaliplatin and relative resistance in a human NSCLC tumor panel *in vitro*. The cell lines used are H460, A549, H838, and H226, which have a wild-type p53; H1975, SkLU1, H2122, and H157, which have a mutated p53; and H1229, which has a null p53.

[0032] Figure 12 is a graph showing the cytotoxicity of DAG and relative resistance in a human NSCLC tumor panel *in vitro*. The cell lines used are H460, A549,

H838, and H226, which have a wild-type p53; H1975, SkLU1, H2122, and H157, which have a mutated p53; and H1229, which has a null p53.

[0033] Figure 13 is a graph showing the cytotoxicity of dianhydrogalactitol ("DAG") and the platinum drugs cisplatin ("cis-Pt") and oxaliplatin ("Oxali-Pt") against engineered HCT-116 tumor models *in vitro*. To better explore dependency of activity on p53 status, the molecularly engineered colorectal HCT-116 models were used. These isogenic models were molecularly engineered to knockout p53 ($p53^{-/-}$) or p21 ($p21^{-/-}$). The $p53^{+/+}$ or $p21^{+/+}$ represent the corresponding control. These IC_{50} values were used to determine resistance of knockout models relative to corresponding controls.

[0034] Figure 14 is a graph showing the resistance factors for dianhydrogalactitol ("DAG") and the platinum drugs cisplatin ("cis-Pt") and oxaliplatin ("Oxali-Pt") in engineered HCT-116 tumor models *in vitro*. The resistance factors in the engineered colorectal HCT-116 models demonstrate that loss of p53 and p21 result in about 2-fold or greater resistance to cisplatin and oxaliplatin, but the resistance to DAG was lower ($p53^{-/-}$) or non-existent ($p21^{-/-}$).

[0035] Figure 15 shows the combination index of dianhydrogalactitol ("DAG") with cisplatin or oxaliplatin in an *in vitro* model of human A549 NSCLC model.

[0036] Figure 16 is a graph showing the effect of dianhydrogalactitol (DAG) in combination with cisplatin or oxaliplatin on cytotoxicity in A549 cells *in vitro*. The left panel shows the results of DAG in combination with cisplatin; the right panel shows the results of DAG in combination with oxaliplatin.

[0037] Figure 17 is a graph showing the effect of dianhydrogalactitol (DAG) in combination with cisplatin or oxaliplatin on cytotoxicity in H460 cells *in vitro*. The left panel shows the results of DAG in combination with cisplatin; the right panel shows the results of DAG in combination with oxaliplatin. With N=3 independent studies with H460 cells, the combination of cisplatin + DAG almost reaches significance for super-additivity, whereas the combination of oxaliplatin + DAG is super-additive. Data are shown as Mean +/- SE.

[0038] Figure 18 is a graph showing the effect of dianhydrogalactitol (DAG) in combination with cisplatin or oxaliplatin on cytotoxicity in H1975 cells *in vitro*. The left panel shows the results of DAG in combination with cisplatin; the right panel shows the

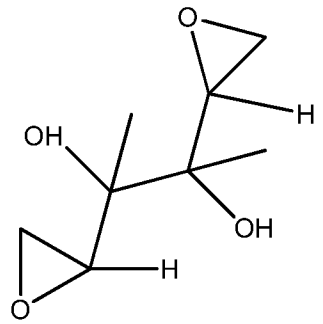
results of DAG in combination with oxaliplatin. With N=3 independent studies with H1975 cells, the combination of cisplatin + DAG is additive, whereas the combination of oxaliplatin + DAG approaches significance for super-additivity. Data are shown as Mean +/- SE.

DETAILED DESCRIPTION OF THE INVENTION

[0039] The compound dianhydrogalactitol (DAG) has been shown to have substantial efficacy in inhibiting the growth of non-small-cell lung carcinoma (NSCLC) cells. In the case of GBM, DAG has proven to be more effective in suppressing the growth of NSCLC cells in a mouse model than cisplatin, the current chemotherapy of choice for NSCLC. As detailed below, DAG can effectively suppress the growth of cancer stem cells (CSCs). DAG acts independently of the MGMT repair mechanism.

[0040] As detailed below, DAG also shows efficacy against ovarian tumor cells. Methods and compositions suitable for use against ovarian cancer are described below.

[0041] The structure of dianhydrogalactitol (DAG) is shown in Formula (I), below.



(I)

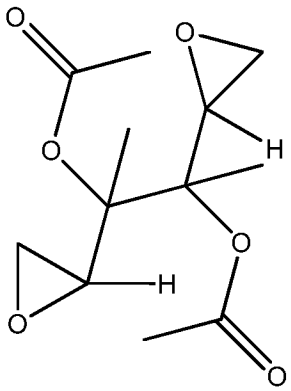
[0042] As detailed below, other substituted hexitols can be used in methods and compositions according to the present invention. In general, the substituted hexitols usable in methods and compositions according to the present invention include galactitols, substituted galacitols, dulcitols, and substituted dulcitols, including dianhydrogalactitol, diacetyldianhydrogalactitol, dibromodulcitol, and derivatives and analogs thereof. Typically, the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol,

and derivatives of dibromodulcitol. Preferably, the substituted hexitol derivative is dianhydrogalactitol.

[0043] These galactitols, substituted galacitols, dulcitols, and substituted dulcitols are either alkylating agents or prodrugs of alkylating agents, as discussed further below.

[0044] Also within the scope of the invention are derivatives of dianhydrogalactitol that, for example, have one or both hydrogens of the two hydroxyl groups of dianhydrogalactitol replaced with lower alkyl, have one or more of the hydrogens attached to the two epoxide rings replaced with lower alkyl, or have the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups replaced with C_2-C_6 lower alkyl or substituted with, for example, halo groups by replacing a hydrogen of the methyl group with, for example a halo group. As used herein, the term "halo group," without further limitation, refers to one of fluoro, chloro, bromo, or iodo. As used herein, the term "lower alkyl," without further limitation, refers to C_1-C_6 groups and includes methyl. The term "lower alkyl" can be further limited, such as "C_2-C_6 lower alkyl," which excludes methyl. The term "lower alkyl", unless further limited, refers to both straight-chain and branched alkyl groups. These groups can, optionally, be further substituted, as described below.

[0045] The structure of diacetyldianhydrogalactitol is shown in Formula (II), below.

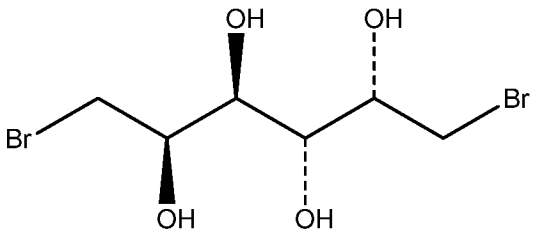


(II)

[0046] Also within the scope of the invention are derivatives of diacetyldianhydrogalactitol that, for example, have one or both of the methyl groups that are part of the acetyl moieties replaced with C_2-C_6 lower alkyl, have one or both of the

hydrogens attached to the epoxide ring replaced with lower alkyl, or have the methyl groups attached to the same carbons that bear the acetyl groups replaced with lower alkyl or substituted with, for example, halo groups by replacing a hydrogen with, for example, a halo group.

[0047] The structure of dibromodulcitol is shown in Formula (III), below. Dibromodulcitol can be produced by the reaction of dulcitol with hydrobromic acid at elevated temperatures, followed by crystallization of the dibromodulcitol. Some of the properties of dibromodulcitol are described in N.E. Mischler et al., "Dibromoducitol," Cancer Treat. Rev. 6: 191-204 (1979), incorporated herein by this reference. In particular, dibromodulcitol, as an α, ω-dibrominated hexitol, dibromodulcitol shares many of the biochemical and biological properties of similar drugs such as dibromomannitol and mannitol myleran. Activation of dibromodulcitol to the diepoxide dianhydrogalactitol occurs *in vivo*, and dianhydrogalactitol may represent a major active form of the drug; this means that dibromogalactitol has many of the properties of a prodrug. Absorption of dibromodulcitol by the oral route is rapid and fairly complete. Dibromodulcitol has known activity in melanoma, breast lymphoma (both Hodgkins and non-Hodgkins), colorectal cancer, acute lymphoblastic leukemia and has been shown to lower the incidence of central nervous system leukemia, non-small cell lung cancer, cervical carcinoma, bladder carcinoma, and metastatic hemangiopericytoma.



(III)

[0048] Also within the scope of the invention are derivatives of dibromodulcitol that, for example, have one or more hydrogens of the hydroxyl groups replaced with lower alkyl, or have one or both of the bromo groups replaced with another halo group such as chloro, fluoro, or iodo.

[0049] In general, for optional substituents at saturated carbon atoms such as those that are part of the structures of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol, the following substituents can be employed: C_6-C_{10} aryl, heteroaryl containing 1-4 heteroatoms selected from N, O, and S, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, cycloalkyl, F, amino (NR^1R^2), nitro, —SR, —S(O)R, —$S(O_2)$R, —$S(O_2)NR^1R^2$, and —$CONR^1R^2$, which can in turn be optionally substituted. Further descriptions of potential optional substituents are provided below.

[0050] Optional substituents as described above that are within the scope of the present invention do not substantially affect the activity of the derivative or the stability of the derivative, particularly the stability of the derivative in aqueous solution. Definitions for a number of common groups that can be used as optional substituents are provided below; however, the omission of any group from these definitions cannot be taken to mean that such a group cannot be used as an optional substituent as long as the chemical and pharmacological requirements for an optional substituent are satisfied.

[0051] As used herein, the term “alkyl” refers to an unbranched, branched, or cyclic saturated hydrocarbyl residue, or a combination thereof, of from 1 to 12 carbon atoms that can be optionally substituted; the alkyl residues contain only C and H when unsubstituted. Typically, the unbranched or branched saturated hydrocarbyl residue is from 1 to 6 carbon atoms, which is referred to herein as “lower alkyl.” When the alkyl residue is cyclic and includes a ring, it is understood that the hydrocarbyl residue includes at least three carbon atoms, which is the minimum number to form a ring. As used herein, the term “alkenyl” refers to an unbranched, branched or cyclic hydrocarbyl residue having one or more carbon-carbon double bonds. As used herein, the term “alkynyl” refers to an unbranched, branched, or cyclic hydrocarbyl residue having one or more carbon-carbon triple bonds; the residue can also include one or more double bonds. With respect to the use of “alkenyl” or “alkynyl,” the presence of multiple double bonds cannot produce an aromatic ring. As used herein, the terms “hydroxyalkyl,” “hydroxyalkenyl,” and “hydroxyalkynyl,” respectively, refer to an alkyl, alkenyl, or alkynyl

group including one or more hydroxyl groups as substituents; as detailed below, further substituents can be optionally included. As used herein, the term "aryl" refers to a monocyclic or fused bicyclic moiety having the well-known characteristics of aromaticity; examples include phenyl and naphthyl, which can be optionally substituted. As used herein, the term "hydroxyaryl" refers to an aryl group including one or more hydroxyl groups as substituents; as further detailed below, further substituents can be optionally included. As used herein, the term "heteroaryl" refers to monocyclic or fused bicylic ring systems that have the characteristics of aromaticity and include one or more heteroatoms selected from O, S, and N. The inclusion of a heteroatom permits aromaticity in 5-membered rings as well as in 6-membered rings. Typical heteroaromatic systems include monocyclic C_5-C_6 heteroaromatic groups such as pyridyl, pyrimidyl, pyrazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, triazolyl, triazinyl, tetrazolyl, tetrazinyl, and imidazolyl, as well as the fused bicyclic moieties formed by fusing one of these monocyclic heteroaromatic groups with a phenyl ring or with any of the heteroaromatic monocyclic groups to form a C_8-C_{10} bicyclic group such as indolyl, benzimidazolyl, indazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, pyrazolylpyridyl, quinazolinyl, quinoxalinyl, cinnolinyl, and other ring systems known in the art. Any monocyclic or fused ring bicyclic system that has the characteristics of aromaticity in terms of delocalized electron distribution throughout the ring system is included in this definition. This definition also includes bicyclic groups where at least the ring that is directly attached to the remainder of the molecule has the characteristics of aromaticity, including the delocalized electron distribution that is characteristic of aromaticity. Typically the ring systems contain 5 to 12 ring member atoms and up to four heteroatoms, wherein the heteroatoms are selected from the group consisting of N, O, and S. Frequently, the monocyclic heteroaryls contain 5 to 6 ring members and up to three heteroatoms selected from the group consisting of N, O, and S; frequently, the bicyclic heteroaryls contain 8 to 10 ring members and up to four heteroatoms selected from the group consisting of N, O, and S. The number and placement of heteroatoms in heteroaryl ring structures is in accordance with the well-known limitations of aromaticity and stability, where stability requires the heteroaromatic group to be stable enough to be exposed to water at

physiological temperatures without rapid degradation. As used herein, the term "hydroxheteroaryl" refers to a heteroaryl group including one or more hydroxyl groups as substituents; as further detailed below, further substituents can be optionally included. As used herein, the terms "haloaryl" and "haloheteroaryl" refer to aryl and heteroaryl groups, respedively, substituted with at least one halo group, where "halo" refers to a halogen selected from the group consisting of fluorine, chlorine, bromine, and iodine, typically, the halogen is selected from the group consisting of chlorine, bromine, and iodine; as detailed below, further substituents can be optionally included. As used herein, the terms "haloalkyl," "haloalkenyl," and "haloalkynyl" refer to alkyl, alkenyl, and alkynyl groups, respectively, substituted with at least one halo group, where "halo" refers to a halogen selected from the group consisting of fluorine, chlorine, bromine, and iodine, typically, the halogen is selected from the group consisting of chlorine, bromine, and iodine; as detailed below, further substituents can be optionally included.

[0052] As used herein, the term "optionally substituted" indicates that the particular group or groups referred to as optionally substituted may have no non-hydrogen substituents, or the group or groups may have one or more non-hydrogen substituents consistent with the chemistry and pharmacological activity of the resulting molecule. If not otherwise specified, the total number of such substituents that may be present is equal to the total number of hydrogen atoms present on the unsubstituted form of the group being described; fewer than the maximum number of such substituents may be present. Where an optional substituent is attached via a double bond, such as a carbonyl oxygen (C=O), the group takes up two available valences on the carbon atom to which the optional substituent is attached, so the total number of substituents that may be included is reduced according to the number of available valiences. As used herein, the term "substituted," whether used as part of "optionally substituted" or otherwise, when used to modify a specific group, moiety, or radical, means that one or more hydrogen atoms are, each, independently of each other, replaced with the same or different substituent or substituents.

[0053] Substituent groups useful for substituting saturated carbon atoms in the specified group, moiety, or radical include, but are not limited to, $—Z^a$, =O, $—OZ^b$, $—SZ^b$, $=S^-$, $—NZ^cZ^c$, $=NZ^b$, $=N—OZ^b$, trihalomethyl, $—CF_3$, —CN, —OCN, —SCN, —NO,

—NO_2, =N_2, —N_3, —$S(O)_2Z^b$, —$S(O)_2NZ^b$, —$S(O_2)O^-$, —$S(O_2)OZ^b$, —$OS(O_2)OZ^b$, —$OS(O_2)O^-$, —$OS(O_2)OZ^b$, —$P(O)(O^-)_2$, —$P(O)(OZ^b)(O^-)$, —$P(O)(OZ^b)(OZ^b)$, —$C(O)Z^b$, —$C(S)Z^b$, —$C(NZ^b)Z^b$, —$C(O)O^-$, —$C(O)OZ^b$, —$C(S)OZ^b$, —$C(O)NZ^cZ^c$, —$C(NZ^b)NZ^cZ^c$, —$OC(O)Z^b$, —$OC(S)Z^b$, —$OC(O)O^-$, —$OC(O)OZ^b$, —$OC(S)OZ^b$, —$NZ^bC(O)Z^b$, —$NZ^bC(S)Z^b$, —$NZ^bC(O)O^-$, —$NZ^bC(O)OZ^b$, —$NZ^bC(S)OZ^b$, —$NZ^bC(O)NZ^cZ^c$, —$NZ^bC(NZ^b)Z^b$, —$NZ^bC(NZ^b)NZ^cZ^c$, wherein Z^a is selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; each Z^b is independently hydrogen or Z^a; and each Z^c is independently Z^b or, alternatively, the two Z^c's may be taken together with the nitrogen atom to which they are bonded to form a 4-, 5-, 6-, or 7-membered cycloheteroalkyl ring structure which may optionally include from 1 to 4 of the same or different heteroatoms selected from the group consisting of N, O, and S. As specific examples, —NZ^cZ^c is meant to include —NH_2, —NH-alkyl, —N-pyrrolidinyl, and —N-morpholinyl, but is not limited to those specific alternatives and includes other alternatives known in the art. Similarly, as another specific example, a substituted alkyl is meant to include —alkylene-O-alkyl, —alkylene-heteroaryl, —alkylene-cycloheteroaryl, —alkylene-$C(O)OZ^b$, —alkylene-$C(O)NZ^bZ^b$, and —CH_2—CH_2—$C(O)$-CH_3, but is not limited to those specific alternatives and includes other alternatives known in the art. The one or more substituent groups, together with the atoms to which they are bonded, may form a cyclic ring, including, but not limited to, cycloalkyl and cycloheteroalkyl.

[0054] Similarly, substituent groups useful for substituting unsaturated carbon atoms in the specified group, moiety, or radical include, but are not limited to, —Z^a, halo, —O^-, —OZ^b, —SZ^b, —S^-, —NZ^cZ^c, trihalomethyl, —CF_3, —CN, —OCN, —SCN, —NO, —NO_2, —N_3, —$S(O)_2Z^b$, —$S(O_2)O^-$, —$S(O_2)OZ^b$, —$OS(O_2)OZ^b$, —$OS(O_2)O^-$, —$P(O)(O^-)_2$, —$P(O)(OZ^b)(O^-)$, —$P(O)(OZ^b)(OZ^b)$, —$C(O)Z^b$, —$C(S)Z^b$, —$C(NZ^b)Z^b$, —$C(O)O^-$, —$C(O)OZ^b$, —$C(S)OZ^b$, —$C(O)NZ^cZ^c$, —$C(NZ^b)NZ^cZ^c$, —$OC(O)Z^b$, —$OC(S)Z^b$, —$OC(O)O^-$, —$OC(O)OZ^b$, —$OC(S)OZ^b$, —$NZ^bC(O)OZ^b$, —$NZ^bC(S)OZ^b$, —$NZ^bC(O)NZ^cZ^c$, —$NZ^bC(NZ^b)Z^b$, and —$NZ^bC(NZ^b)NZ^cZ^c$, wherein Z^a, Z^b, and Z^c are as defined above.

[0055] Similarly, substituent groups useful for substituting nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, but are not limited to, —Z^a, halo, —O^-,

—OZ^b, —SZ^b, —S^-, —NZ^cZ^c, trihalomethyl, —CF_3, —CN, —OCN, —SCN, —NO, —NO_2, —$S(O)_2Z^b$, —$S(O_2)O^-$, —$S(O_2)OZ^b$, —$OS(O_2)OZ^b$, —$OS(O_2)O^-$, —$P(O)(O^-)_2$, —$P(O)(OZ^b)(O^-)$, —$P(O)(OZ^b)(OZ^b)$, —$C(O)Z^b$, —$C(S)Z^b$, —$C(NZ^b)Z^b$, —$C(O)OZ^b$, —$C(S)OZ^b$, —$C(O)NZ^cZ^c$, —$C(NZ^b)NZ^cZ^c$, —$OC(O)Z^b$, —$OC(S)Z^b$, —$OC(O)OZ^b$, —$OC(S)OZ^b$, —$NZ^bC(O)Z^b$, —$NZ^bC(S)Z^b$, —$NZ^bC(O)OZ^b$, —$NZ^bC(S)OZ^b$, —$NZ^bC(O)NZ^cZ^c$, —$NZ^bC(NZ^b)Z^b$, and —$NZ^bC(NZ^b)NZ^cZ^c$, wherein Z^a, Z^b, and Z^c are as defined above.

[0056] The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers such as E and Z), enantiomers or diastereomers. The invention includes each of the isolated stereoisomeric forms (such as the enantiomerically pure isomers, the E and Z isomers, and other alternatives for stereoisomers) as well as mixtures of stereoisomers in varying degrees of chiral purity or percentage of E and Z, including racemic mixtures, mixtures of diastereomers, and mixtures of E and Z isomers, unless a specific stereoisomer is specified. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The invention includes each of the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity, including racemic mixtures. It also encompasses the various diastereomers. Other structures may appear to depict a specific isomer, but that is merely for convenience, and is not intended to limit the invention to the depicted isomer. When the chemical name does not specify the isomeric form of the compound, it denotes any one of the possible isomeric forms or mixtures of those isomeric forms of the compound.

[0057] The compounds may also exist in several tautomeric forms, and the depiction herein of one tautomer is for convenience only, and is also understood to encompass other tautomers of the form shown. Accordingly, the chemical structures

depicted herein encompass all possible tautomeric forms of the illustrated compounds. The term "tautomer" as used herein refers to isomers that change into one another with great ease so that they can exist together in equilibrium; the equilibrium may strongly favor one of the tautomers, depending on stability considerations. For example, ketone and enol are two tautomeric forms of one compound.

[0058] As used herein, the term “solvate” means a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute), or an aggregate that consists of a solute ion or molecule, i.e., a compound of the invention, with one or more solvent molecules. When water is the solvent, the corresponding solvate is “hydrate.” Examples of hydrate include, but are not limited to, hemihydrate, monohydrate, dihydrate, trihydrate, hexahydrate, and other water-containing species. It should be understood by one of ordinary skill in the art that the pharmaceutically acceptable salt, and/or prodrug of the present compound may also exist in a solvate form. The solvate is typically formed via hydration which is either part of the preparation of the present compound or through natural absorption of moisture by the anhydrous compound of the present invention.

[0059] As used herein, the term “ester” means any ester of a present compound in which any of the --COOH functions of the molecule is replaced by a --COOR function, in which the R moiety of the ester is any carbon-containing group which forms a stable ester moiety, including but not limited to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl and substituted derivatives thereof. The hydrolysable esters of the present compounds are the compounds whose carboxyls are present in the form of hydrolysable ester groups. That is, these esters are pharmaceutically acceptable and can be hydrolyzed to the corresponding carboxyl acid in vivo.

[0060] In addition to the substituents described above, alkyl, alkenyl and alkynyl groups can alternatively or in addition be substituted by C_1-C_8 acyl, C_2-C_8 heteroacyl, C_6-C_{10} aryl, C_3-C_8 cycloalkyl, C_3-C_8 heterocyclyl, or C_5-C_{10} heteroaryl, each of which can be optionally substituted. Also, in addition, when two groups capable of forming a ring having 5 to 8 ring members are present on the same or adjacent atoms, the two groups

can optionally be taken together with the atom or atoms in the substituent groups to which they are attached to form such a ring.

[0061] "Heteroalkyl," "heteroalkenyl," and "heteroalkynyl" and the like are defined similarly to the corresponding hydrocarbyl (alkyl, alkenyl and alkynyl) groups, but the 'hetero' terms refer to groups that contain 1-3 O, S or N heteroatoms or combinations thereof within the backbone residue; thus at least one carbon atom of a corresponding alkyl, alkenyl, or alkynyl group is replaced by one of the specified heteroatoms to form, respectively, a heteroalkyl, heteroalkenyl, or heteroalkynyl group. For reasons of chemical stability, it is also understood that, unless otherwise specified, such groups do not include more than two contiguous heteroatoms except where an oxo group is present on N or S as in a nitro or sulfonyl group.

[0062] While "alkyl" as used herein includes cycloalkyl and cycloalkylalkyl groups, the term "cycloalkyl" may be used herein to describe a carbocyclic non-aromatic group that is connected via a ring carbon atom, and "cycloalkylalkyl" may be used to describe a carbocyclic non-aromatic group that is connected to the molecule through an alkyl linker.

[0063] Similarly, "heterocyclyl" may be used to describe a non-aromatic cyclic group that contains at least one heteroatom (typically selected from N, O and S) as a ring member and that is connected to the molecule via a ring atom, which may be C (carbon-linked) or N (nitrogen-linked); and "heterocyclylalkyl" may be used to describe such a group that is connected to another molecule through a linker. The heterocyclyl can be fully saturated or partially saturated, but non-aromatic. The sizes and substituents that are suitable for the cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl groups are the same as those described above for alkyl groups. The heterocyclyl groups typically contain 1, 2 or 3 heteroatoms, selected from N, O and S as ring members; and the N or S can be substituted with the groups commonly found on these atoms in heterocyclic systems. As used herein, these terms also include rings that contain a double bond or two, as long as the ring that is attached is not aromatic. The substituted cycloalkyl and heterocyclyl groups also include cycloalkyl or heterocyclic rings fused to an aromatic ring or heteroaromatic ring, provided the point of

attachment of the group is to the cycloalkyl or heterocyclyl ring rather than to the aromatic/heteroaromatic ring.

[0064] As used herein, "acyl" encompasses groups comprising an alkyl, alkenyl, alkynyl, aryl or arylalkyl radical attached at one of the two available valence positions of a carbonyl carbon atom, and heteroacyl refers to the corresponding groups wherein at least one carbon other than the carbonyl carbon has been replaced by a heteroatom chosen from N, O and S.

[0065] Acyl and heteroacyl groups are bonded to any group or molecule to which they are attached through the open valence of the carbonyl carbon atom. Typically, they are C_1-C_8 acyl groups, which include formyl, acetyl, pivaloyl, and benzoyl, and C_2-C_8 heteroacyl groups, which include methoxyacetyl, ethoxycarbonyl, and 4-pyridinoyl.

[0066] Similarly, "arylalkyl" and "heteroarylalkyl" refer to aromatic and heteroaromatic ring systems which are bonded to their attachment point through a linking group such as an alkylene, including substituted or unsubstituted, saturated or unsaturated, cyclic or acyclic linkers. Typically the linker is C_1-C_8 alkyl. These linkers may also include a carbonyl group, thus making them able to provide substituents as an acyl or heteroacyl moiety. An aryl or heteroaryl ring in an arylalkyl or heteroarylalkyl group may be substituted with the same substituents described above for aryl groups. Preferably, an arylalkyl group includes a phenyl ring optionally substituted with the groups defined above for aryl groups and a C_1-C_4 alkylene that is unsubstituted or is substituted with one or two C_1-C_4 alkyl groups or heteroalkyl groups, where the alkyl or heteroalkyl groups can optionally cyclize to form a ring such as cyclopropane, dioxolane, or oxacyclopentane. Similarly, a heteroarylalkyl group preferably includes a C_5-C_6 monocyclic heteroaryl group that is optionally substituted with the groups described above as substituents typical on aryl groups and a C_1-C_4 alkylene that is unsubstituted or is substituted with one or two C_1-C_4 alkyl groups or heteroalkyl groups, or it includes an optionally substituted phenyl ring or C_5-C_6 monocyclic heteroaryl and a C_1-C_4 heteroalkylene that is unsubstituted or is substituted with one or two C_1-C_4 alkyl or heteroalkyl groups, where the alkyl or heteroalkyl groups can optionally cyclize to form a ring such as cyclopropane, dioxolane, or oxacyclopentane.

[0067] Where an arylalkyl or heteroarylalkyl group is described as optionally substituted, the substituents may be on either the alkyl or heteroalkyl portion or on the aryl or heteroaryl portion of the group. The substituents optionally present on the alkyl or heteroalkyl portion are the same as those described above for alkyl groups generally; the substituents optionally present on the aryl or heteroaryl portion are the same as those described above for aryl groups generally.

[0068] "Arylalkyl" groups as used herein are hydrocarbyl groups if they are unsubstituted, and are described by the total number of carbon atoms in the ring and alkylene or similar linker. Thus a benzyl group is a C7-arylalkyl group, and phenylethyl is a C8-arylalkyl.

[0069] "Heteroarylalkyl" as described above refers to a moiety comprising an aryl group that is attached through a linking group, and differs from "arylalkyl" in that at least one ring atom of the aryl moiety or one atom in the linking group is a heteroatom selected from N, O and S. The heteroarylalkyl groups are described herein according to the total number of atoms in the ring and linker combined, and they include aryl groups linked through a heteroalkyl linker; heteroaryl groups linked through a hydrocarbyl linker such as an alkylene; and heteroaryl groups linked through a heteroalkyl linker. Thus, for example, C7-heteroarylalkyl would include pyridylmethyl, phenoxy, and N-pyrrolylmethoxy.

[0070] "Alkylene" as used herein refers to a divalent hydrocarbyl group; because it is divalent, it can link two other groups together. Typically it refers to —$(CH_2)_n$— where n is 1-8 and preferably n is 1-4, though where specified, an alkylene can also be substituted by other groups, and can be of other lengths, and the open valences need not be at opposite ends of a chain.

[0071] In general, any alkyl, alkenyl, alkynyl, acyl, or aryl or arylalkyl group that is contained in a substituent may itself optionally be substituted by additional substituents. The nature of these subtituents is similar to those recited with regard to the primary substituents themselves if the substituents are not otherwise described.

[0072] "Amino" as used herein refers to —NH_2, but where an amino is described as "substituted" or "optionally substituted", the term includes NR′R″ wherein each R′ and R″ is independently H, or is an alkyl, alkenyl, alkynyl, acyl, aryl, or arylalkyl group,

and each of the alkyl, alkenyl, alkynyl, acyl, aryl, or arylalkyl groups is optionally substituted with the substituents described herein as suitable for the corresponding group; the R′ and R″ groups and the nitrogen atom to which they are attached can optionally form a 3- to 8-membered ring which may be saturated, unsaturated or aromatic and which contains 1-3 heteroatoms independently selected from N, O and S as ring members, and which is optionally substituted with the substituents described as suitable for alkyl groups or, if NR′R″ is an aromatic group, it is optionally substituted with the substituents described as typical for heteroaryl groups.

[0073] As used herein, the term “carbocycle,” “carbocyclyl,” or “carbocyclic” refers to a cyclic ring containing only carbon atoms in the ring, whereas the term “heterocycle” or “heterocyclic” refers to a ring comprising a heteroatom. The carbocyclyl can be fully saturated or partially saturated, but non-aromatic. For example, the carbocyclyl encompasses cycloalkyl. The carbocyclic and heterocyclic structures encompass compounds having monocyclic, bicyclic or multiple ring systems; and such systems may mix aromatic, heterocyclic, and carbocyclic rings. Mixed ring systems are described according to the ring that is attached to the rest of the compound being described.

[0074] As used herein, the term “heteroatom” refers to any atom that is not carbon or hydrogen, such as nitrogen, oxygen or sulfur. When it is part of the backbone or skeleton of a chain or ring, a heteroatom must be at least divalent, and will typically be selected from N, O, P, and S.

[0075] As used herein, the term “alkanoyl” refers to an alkyl group covalently linked to a carbonyl (C=O) group. The term “lower alkanoyl” refers to an alkanoyl group in which the alkyl portion of the alkanoyl group is C_1-C_6. The alkyl portion of the alkanoyl group can be optionally substituted as described above. The term “alkylcarbonyl” can alternatively be used. Similarly, the terms “alkenylcarbonyl” and “alkynylcarbonyl” refer to an alkenyl or alkynyl group, respectively, linked to a carbonyl group.

[0076] As used herein, the term “alkoxy” refers to an alkyl group covalently linked to an oxygen atom; the alkyl group can be considered as replacing the hydrogen atom of a hydroxyl group. The term “lower alkoxy” refers to an alkoxy group in which

the alkyl portion of the alkoxy group is C_1-C_6. The alkyl portion of the alkoxy group can be optionally substituted as described above. As used herein, the term "haloalkoxy" refers to an alkoxy group in which the alkyl portion is substituted with one or more halo groups.

[0077] As used herein, the term "sulfo" refers to a sulfonic acid (—SO_3H) substituent.

[0078] As used herein, the term "sulfamoyl" refers to a substituent with the structure —$S(O_2)NH_2$, wherein the nitrogen of the NH_2 portion of the group can be optionally substituted as described above.

[0079] As used herein, the term "carboxyl" refers to a group of the structure —$C(O_2)H$.

[0080] As used herein, the term "carbamyl" refers to a group of the structure —$C(O_2)NH_2$, wherein the nitrogen of the NH_2 portion of the group can be optionally substituted as described above.

[0081] As used herein, the terms "monoalkylaminoalkyl" and "dialkylaminoalkyl" refer to groups of the structure —Alk_1-NH-Alk_2 and —Alk_1-N(Alk_2)(Alk_3), wherein Alk_1, Alk_2, and Alk_3 refer to alkyl groups as described above.

[0082] As used herein, the term "alkylsulfonyl" refers to a group of the structure —$S(O)_2$-Alk wherein Alk refers to an alkyl group as described above. The terms "alkenylsulfonyl" and "alkynylsulfonyl" refer analogously to sulfonyl groups covalently bound to alkenyl and alkynyl groups, respectively. The term "arylsulfonyl" refers to a group of the structure —$S(O)_2$-Ar wherein Ar refers to an aryl group as described above. The term "aryloxyalkylsulfonyl" refers to a group of the structure —$S(O)_2$-Alk-O-Ar, where Alk is an alkyl group as described above and Ar is an aryl group as described above. The term "arylalkylsulfonyl" refers to a group of the structure —$S(O)_2$-AlkAr, where Alk is an alkyl group as described above and Ar is an aryl group as described above.

[0083] As used herein, the term "alkyloxycarbonyl" refers to an ester substituent including an alkyl group wherein the carbonyl carbon is the point of attachment to the molecule. An example is ethoxycarbonyl, which is $CH_3CH_2OC(O)$—. Similarly, the terms "alkenyloxycarbonyl," "alkynyloxycarbonyl," and "cycloalkylcarbonyl" refer to

similar ester substituents including an alkenyl group, alkenyl group, or cycloalkyl group respectively. Similarly, the term "aryloxycarbonyl" refers to an ester substituent including an aryl group wherein the carbonyl carbon is the point of attachment to the molecule. Similarly, the term "aryloxyalkylcarbonyl" refers to an ester substituent including an alkyl group wherein the alkyl group is itself substituted by an aryloxy group.

[0084] Other combinations of substituents are known in the art and, are described, for example, in United States Patent No. 8,344,162 to Jung et al., incorporated herein by this reference. For example, the term "thiocarbonyl" and combinations of substituents including "thiocarbonyl" include a carbonyl group in which a double-bonded sulfur replaces the normal double-bonded oxygen in the group. The term "alkylidene" and similar terminology refer to an alkyl group, alkenyl group, alkynyl group, or cycloalkyl group, as specified, that has two hydrogen atoms removed from a single carbon atom so that the group is double-bonded to the remainder of the structure.

[0085] For the aspects described below relating to improvement in the therapeutic employment of a substituted hexitol derivative, typically, the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol, unless otherwise specified. Preferably, the substituted hexitol derivative is dianhydrogalactitol, unless otherwise specified. In some cases, derivatives of dianhydrogalactitol such as compound analogs or prodrugs are preferred, as stated below.

[0086] One aspect of the present invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations to the time that the compound is administered, the use of dose-modifying agents that control the rate of metabolism of the compound, normal tissue protective agents, and other alterations. General examples include: variations of infusion schedules (e.g., bolus i.v. versus continuous infusion), the use of lymphokines (e.g., G-CSF, GM-CSF, EPO) to increase leukocyte count for improved immune response or for preventing anemia caused by myelosuppressive agents, or the use of rescue agents such as leucovorin for 5-FU or thiosulfate for cisplatin treatment. Specific inventive examples for a substituted hexitol

derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: continuous i.v. infusion for hours to days; biweekly administration; doses greater than 5 mg/m^2/day; progressive escalation of dosing from 1 mg/m^2/day based on patient tolerance; doses less than 1 mg/m^2 for greater than 14 days; use of caffeine to modulate metabolism; use of isoniazid to modulate metabolism; single and multiple doses escalating from 5 mg/m^2/day via bolus; oral doses below 30 or above 130 mg/m^2; oral dosages up to 40 mg/m^2 for 3 days and then a nadir/recovery period of 18-21 days; dosing at a lower level for an extended period (e.g., 21 days); dosing at a higher level; dosing with a nadir/recovery period longer than 21 days; the use of a substituted hexitol derivative such as dianhydrogalactitol as a single cytotoxic agent, typically at 30 mg/m^2/day $\times$ 5 days, repeated monthly; dosing at 3 mg/kg; the use of a substituted hexitol derivative such as dianhydrogalactitol in combination therapy, typically at 30 mg/m^2/day $\times$ 5 days; or dosing at 40 mg/day $\times$ 5 days in adult patients, repeated every two weeks.

[0087] Another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations in the route by which the compound is administered. General examples include: changing route from oral to intravenous administration and vice versa; or the use of specialized routes such as subcutaneous, intramuscular, intraarterial, intraperitoneal, intralesional, intralymphatic, intratumoral, intrathecal, intravesicular, intracranial. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: topical administration; oral administration; slow-release oral delivery; intrathecal administration; intraarterial administration; continuous infusion; intermittent infusion; intravenous administration; or administration through a longer infusion; or administration through IV push.

[0088] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by changes in the schedule of administration. General examples include: daily administration, biweekly administration, or weekly administration. Specific inventive examples for a substituted hexitol derivative such as

dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: daily administration; weekly administration; weekly administration for three weeks; biweekly administration; biweekly administration for three weeks with a 1-2 week rest period; intermittent boost dose administration; or daily administration for one week for multiple weeks.

[0089] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations in the stage of disease at diagnosis/progression that the compound is administered. General examples include: the use of chemotherapy for non-resectable local disease, prophylactic use to prevent metastatic spread or inhibit disease progression or conversion to more malignant stages. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: use in an appropriate disease stage for NSCLC or ovarian cancer; use of the substituted hexitol derivative such as dianhydrogalactitol with angiogenesis inhibitors such as Avastin, a VEGF inhibitor, to prevent or limit metastatic spread; the use of a substituted hexitol derivative such as dianhydrogalactitol for newly diagnosed disease; the use of a substituted hexitol derivative such as dianhydrogalactitol for recurrent disease; or the use of a substituted hexitol derivative such as dianhydrogalactitol for resistant or refractory disease.

[0090] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations to the type of patient that would best tolerate or benefit from the use of the compound. General examples include: use of pediatric doses for elderly patients, altered doses for obese patients; exploitation of co-morbid disease conditions such as diabetes, cirrhosis, or other conditions that may uniquely exploit a feature of the compound. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: patients with a disease condition characterized by a high level of a metabolic enzyme selected from the group consisting of histone deacetylase and ornithine decarboxylase; patients with a low or high susceptibility to a condition selected

from the group consisting of thrombocytopenia and neutropenia; patients intolerant of GI toxicities; patients characterized by over- or under-expression of a gene selected from the group consisting of c-Jun, a GPCR, a signal transduction protein, VEGF, a prostate-specific gene, and a protein kinase; prostate-specific gene, and a protein kinase; patients characterized by a mutation in EGFR including, but not limited to, EGFR Variant III; patients being administered a platinum-based drug as combination therapy; patients who do not have EGFR mutations and thus are less likely to respond to tyrosine kinase inhibitors (TKI); patients who have become resistant to TKI treatment; patients who have the *BIM* co-deletion mutation and thus are less likely to respond to TKI treatment; patients who have become resistant to platinum-based drug treatment; or patients with brain metastases.

[0091] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by more precise identification of a patient's ability to tolerate, metabolize and exploit the use of the compound as associated with a particular phenotype of the patient. General examples include: use of diagnostic tools and kits to better characterize a patient's ability to process/metabolize a chemotherapeutic agent or the susceptibility of the patient to toxicity caused by potential specialized cellular, metabolic, or organ system phenotypes. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular phenotype; use of a method for measurement of a marker selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a protein that is a gene product of jun, and a protein kinase; surrogate compound testing; or low dose pre-testing for enzymatic status.

[0092] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by more precise identification of a patient's ability to tolerate, metabolize and exploit the use of the compound as associated with a particular genotype of the patient. General examples include: biopsy samples of tumors or normal tissues (e.g., glial cells or other cells of the central nervous system) that may also be

taken and analyzed to specifically tailor or monitor the use of a particular drug against a gene target; studies of unique tumor gene expression patterns; or analysis of SNP's (single nucleotide polymorphisms), to enhance efficacy or to avoid particular drug-sensitive normal tissue toxicities. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: diagnostic tools, techniques, kits and assays to confirm a patient's particular genotype; gene/protein expression chips and analysis; Single Nucleotide Polymorphisms (SNP's) assessment; SNP's for histone deacetylase, ornithine decarboxylase, GPCR's, protein kinases, telomerase, or jun; identification and measurement of metabolism enzymes and metabolites; determination of mutation of PDGFRA gene; determination of mutation of IDH1 gene; determination of mutation of NF1 gene; determination of copy number of the EGFR gene; determination of status of methylation of promoter of MGMT gene; use for disease characterized by an unmethylated promoter region of the MGMT gene; use for disease characterized by a methylated promoter region of the MGMT gene; use for disease characterized by high expression of MGMT; use for disease characterized by low expression of MGMT; or use for disease characterized by EML4-ALK translocations.

[0093] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by specialized preparation of a patient prior to or after the use of a chemotherapeutic agent. General examples include: induction or inhibition of metabolizing enzymes, specific protection of sensitive normal tissues or organ systems. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use of colchicine or analogs; use of diuretics such as probenecid; use of a uricosuric; use of uricase; non-oral use of nicotinamide; sustained release forms of nicotinamide; use of inhibitors of poly (ADP ribose) polymerase; use of caffeine; leucovorin rescue; infection control; antihypertensives.

[0094] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by use of additional drugs or procedures to prevent

or reduce potential side-effects or toxicities. General examples include: the use of anti-emetics, anti-nausea, hematological support agents to limit or prevent neutropenia, anemia, thrombocytopenia, vitamins, antidepressants, treatments for sexual dysfunction, and other supportive techniques. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use of colchicine or analogs; use of diuretics such as probenecid; use of a uricosuric; use of uricase; non-oral use of nicotinamide; use of sustained release forms of nicotinamide; use of inhibitors of poly ADP-ribose polymerase; use of caffeine; leucovorin rescue; use of sustained release allopurinol; non-oral use of allopurinol; use of bone marrow transplants; use of a blood cell stimulant; use of blood or platelet infusions; use of filgrastim, G-CSF, or GM-CSF; use of pain management techniques; use of anti-inflammatories; use of fluids; use of corticosteroids; use of insulin control medications; use of antipyretics; use of anti-nausea treatments; use of anti-diarrheal treatment; use of N-acetylcysteine; or use of antihistamines.

[0095] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by the use of monitoring drug levels after dosing in an effort to maximize a patient's drug plasma level, to monitor the generation of toxic metabolites, monitoring of ancillary medicines that could be beneficial or harmful in terms of drug–drug interactions. General examples include: the monitoring of drug plasma protein binding, and monitoring of other pharmacokinetic or pharmacodynamic variables. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: multiple determinations of drug plasma levels; or multiple determinations of metabolites in the blood or urine.

[0096] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by exploiting unique drug combinations that may provide a more than additive or synergistic improvement in efficacy or side-effect management. Specific inventive examples for a substituted hexitol derivative such as

dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: use with topoisomerase inhibitors; use with fraudulent nucleosides; use with fraudulent nucleotides; use with thymidylate synthetase inhibitors; use with signal transduction inhibitors; use with cisplatin, oxaliplatin, or other platinum analogs; use with alkylating agents such as the nitrosoureas (BCNU, Gliadel wafers, CCNU, nimustine (ACNU), bendamustine (Treanda)); use with alkylating agents that damage DNA at a different place than does DAG (TMZ, BCNU, CCNU, and other alkylating agents all damage DNA at O^6 of guanine, whereas DAG cross-links at N^7); use with a monofunctional alkylating agent; use with a bifunctional alkylating agent; use with anti-tubulin agents; use with antimetabolites; use with berberine; use with apigenin; use with amonafide; use with colchicine or analogs; use with genistein; use with etoposide; use with cytarabine; use with camptothecins; use with vinca alkaloids; use with topoisomerase inhibitors; use with 5-fluorouracil; use with curcumin; use with NF-κB inhibitors; use with rosmarinic acid; use with mitoguazone; use with tetrandrine; use with temozolomide (TMZ); use with biological therapies such as antibodies such as Avastin (a VEGF inhibitor), Rituxan, Herceptin, Erbitux; use with epidermal growth factor receptor (EGFR) inhibitors; use with tyrosine kinase inhibitors; use with poly (ADP-ribose) polymerase (PARP) inhibitors; or use with cancer vaccine therapy. The ability to be more than additive or synergistic is particularly significant with respect to the combination of a substituted hexitol derivative such as dianhydrogalactitol with cisplatin, oxaliplatin, or other platinum-containing chemotherapeutic agents.

[0097] When methods according to the present invention are intended for treatment of ovarian cancer, drug combinations can include the use of a substituted hexitol derivative as described above together with an additional agent that possesses anti-neoplastic activity against ovarian tumors. Such additional agents include, but are not limited to, paclitaxel, docetaxel, cisplatin, carboplatin, topotecan, gemcitabine, bleomycin, etoposide, doxorubicin (which can be used in a pegylated liposomal form), tamoxifen, letrozole, olaparib, selumetinib, mTOR inhibitors, PI3 kinase inhibitors, and trichostatin A.

[0098] Additional agents that possess anti-neoplastic activity against NSCLC are known in the art. These additional agents can be included in drug combinations

according to the present invention in a therapeutically effective quantity together with a therapeutically effective quantity of a substituted hexitol derivative as described above. One or more than one of these additional agents can be used. These additional agents can be used together with one or more of the agents as described above for activity against NSCLC in drug combinations including a substituted hexitol derivative such as dianhydrogalactitol or diacetyldianhydrogalactitol. Collectively, these agents are referred to herein as "Additional Secondary Agents with Activity Against NSCLC." These agents include the following: United States Patent No. 8,841,277 to Nguyen et al. discloses the use of 5-azacytidine. United States Patent No. 8,741,889 to Boylan et al. discloses the use of a γ-secretase inhibitor. United States Patent No. 8,575,191 to Chen et al. discloses the use of a pyrroloquinolinyl-pyrrole-2,5-dione compound in combination with an EGFR inhibitor. United States Patent No. 8,529,900 to Alifano et al. discloses the use of an inhibitor of the neurotensin activation of the neurotensin receptor 1 (NTSR1). United States Patent No. 5,795,870 to Narita et al. discloses the use of 14- or 15-membered-ring macrolide compounds such as clarithromycin or erythromycin B. United States Patent No. 5,756,512 to Johnson discloses the use of water-soluble camptothecin analogs. United States Patent No. 4,853,221 to Elslager et al. discloses the use of 5-methyl-6-[[(3,4,5-trimethoxyphenyl)amino]-methyl]-2,4-quinazolinediamine (trimetrexate). United States Patent No. 8,987,461 to Nie et al. discloses the use of substituted pyrazolylpyridine, pyrazolylpyridazine, and pyrazolylpyrimidine derivatives. United States Patent No. 8,987,412 to Arora et al. discloses the use of hydrogen bond surrogate macrocyclic peptides. United States Patent No. 8,987,281 to Reddy et al. discloses the use of folate-vinca conjugates. United States Patent No. 8,987,280 to Dotson et al. discloses the use of pyrazolopyrimidine PIK3 inhibitors, including 4-(3,4-dimethoxyphenoxy)-6-(1H-indazol-4-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidine; 6-(1H-indazol-4-yl)-1-methyl-4-(4-(methylsulfonyl)phenoxy)-1H-pyrazolo[3,4-d]pyrimidine; N-(3-(6-(1H-indazol-4-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl)methanesulfonamide; 6-(1H-indazol-4-yl)-4-(3-(methoxymethyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidine; 3-(6-(1H-indazol-4-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)benzonitrile; 3-(6-(1H-indazol-4-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-N-methylbenzamide; 6-(1H-indazol-4-yl)-

4-(3-methoxyphenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidine; N-(3-(6-(1H-indazol-4-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)phenyl)acetamide; 6-(1H-indazol-4-yl)-1-methyl-4-(4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine; 6-(1H-indazol-4-yl)-4-(4-methoxyphenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidine; 4-(3,4-dimethoxyphenyl)-6-(1H-indazol-4-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidine; 6-(1H-indazol-4-yl)-1-methyl-4-(pyridin-3-yloxy)-1H-pyrazolo[3,4-d]pyrimidine; 6-(1H-indazol-4-yl)-4-(3-methoxyphenoxy)-1-methyl-1H-pyrazolo[3,4-d]pyrimidine; and 6-(1H-indazol-4-yl)-N-(3-methoxyphenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine). 8,987,267 to Reddy et al. discloses the use of 2-substituted-8-alkyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitriles including 8-cyclopentyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile; 8-cyclohexyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile; 8-cyclopentyl-2-((3,5-dimethoxyphenyl)amino)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile; 8-cyclopentyl-7-oxo-2-((3,4,5-trimethoxyphenyl)amino)-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile; and 8-cyclopentyl-2-((4-morpholinopheny)amino)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile. United States Patent No. 8,987,260 to Chuckowree et al. discloses the use of 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine bismesylate. United States Patent No. 8,987,257 to Radetich et al. discloses the use of morpholinylpurine derivatives including 3-[2-((2S,6R)-2,6-dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol; 2,6-bis-((S)-3-methyl-morpholin-4-yl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)-9H-purine; {2-fluoro-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol; 2-(4,4-difluoro-piperidin-1-yl)-8-(1H-indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine; 5-[2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-1,3-dihydro-benzoimidazol-2-one; {5-[2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-2-methoxy-phenyl}-methanol; 8-(1H-indol-4-yl)-2-morpholin-4-yl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine; 2-methoxy-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-benzoic acid; {4-chloro-3-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol; 3-(2,6-di-morpholin-4-yl-9H-purin-8-yl)-benzylamine; 1-{3-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-ethanol; 2,6-di-morpholin-4-yl-8-(1H-pyrrolo[3,2-

b]pyridin-6-yl)-9H-purine; 8-(1H-indol-6-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine; 8-(1H-indol-4-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine; 1-[8-(1H-indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purin-2-yl]-piperidin-4-ol; {3-[2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-5-methoxy-phenyl}-methanol; and 8-(1H-indol-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine. United States Patent No. 8,980,955 to Turchi et al. discloses the use of small molecule inhibitors of Replication Protein A including substituted haloester isoborneols. United States Patent No. 8,980,824 to Cong et al. discloses the use of tubulysins as anti-mitotic agents. United States Patent No. 8,975,401 to Qian et al. discloses the use of quinazoline-based EGFR inhibitors containing a zinc binding moiety. United States Patent No. 8,975,265 to Ince et al. discloses the use of substituted imidazo[1,2-a]pyrimidines and substituted imidazo[1,2-a]pyridines. United States Patent No. 8,975,260 to Currie et al. discloses the use of pyridazinones as Btk kinase inhibitors. United States Patent No. 8,975,248 to Zaknoen et al. discloses the use of 7-*t*-butoxyiminomethylcamptothecin in combination with paclitaxel, epothilone B, cisplatin, carboplatin, {6-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-((R)-1-phenyl-ethyl)-amine, everolimus, imatinib, or bortezomib. United States Patent No. 8,969,401 to Maier et al. discloses the use of sulfonylpyrroles as HDAC inhibitors, including (E)-N-hydroxy-3-[1-(toluene-4-sulfonyl)-1-H-pyrrol-3-yl]-acrylamide; N-hydroxy-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylamide; (E)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide; (E)-N-(2-amino-phenyl)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide; (E)-N-(2-amino-phenyl)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylamide; (E)-N-(2-amino-phenyl)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide; (E)-N-hydroxy-3-(1-[4-(([2-(1H-indol-2-yl)-ethyl]-methyl-amino)-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylamide; (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide; and (E)-N-hydroxy-3-[1-(4-{[(pyridin-3-ylmethyl)-amino]-methyl}-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide. United States Patent No. 8,969,379 to Furitsu et al. discloses the use of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide. United States Patent No. 8,969,372 to Huesca et al. discloses the use of 2,4,5-trisubstituted

arylimidazoles. United States Patent No. 8,962,637 to McAllister et al. discloses the use of aromatic bicyclic compounds with pyrimidine and pyridine moieties that are dual c-SRC/JAK inhibitors, including N-(4-methyl-3-{2-[4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-phenyl)-3-trifluoromethyl-benzamide; N-(4-methyl-3-{2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-phenyl)-3-trifluoromethyl-benzamide; 5-{6-[2-methyl-5-(3-trifluoromethyl-benzoylamino)-phenyl]-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidin-2-ylamino}-pyridine-2-carboxylic acid cyclopropylamide; N-{3-[2-(4-cyclopropylsulfamoyl-phenylamino)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-methyl-phenyl}-3-trifluoromethyl-benzamide; N-(4-chloro-3-{2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-5-oxo-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-phenyl)-3-trifluoromethyl-benzamide; 4-trifluoromethyl-pyridine-2-carboxylic acid {4-chloro-3-[2-(4-methylcarbamoyl-phenylamino)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-phenyl}-amide; 4,4,4-trifluoro-3-methyl-N-[4-methyl-3-(2-{4-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenylamino}-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-phenyl]-butyramide; and 1-cyclopentyl-3-(4-methyl-3-{2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl}-phenyl)-urea. United States Patent No. 8,962,620 to Kuntz et al. discloses the use of substituted 6,5-fused bicyclic heteroaryl compounds to prevent aberrant H3-K27 histone methylation, including N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-(2,5-dimethylthiophen-3-yl)-1-isopropyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide; 6-(2,3-dihydro-1,4-benzodioxin-6-yl)-N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-1-(1-methylethyl)-1H-pyrazolo[3,4-b]pyridine-4-carboxamide; 6-cyclopropyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide; N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-1,3,6-trimethyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide; N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-6-methyl-1-(1-methylethyl)-1H-pyrazolo[3,4-b]pyridine-4-carboxamide; and 6-cyclopropyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-isopropyl-1H-pyrazolo[3,4-b]pyridine-4-carboxamide. United States Patent No. 8,962,619 to Ashwell et al. discloses the use of substituted imidazopyridinyl-aminopyridine compounds. United States Patent No. 8,962,609 to Perrior et al. discloses the use of pyrimidine compounds as inhibitors of protein kinases

IKKε and/or TBK-1, including 5-(2-phenylamino-pyrimidin-4-yl)-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(pyridin-4-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(pyridin-2-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 2-pyrrolidin-1-yl-5-[2-(3 -trifluoromethyl-phenylamino)-pyrimidin-4-yl]-benzonitrile; 2-[4-(3-cyano-4-pyrrolidin-1-yl-phenyl)-pyrimidin-2-ylamino]-oxazole-5-carboxylic acid amide; 5-[2-(5-methyl-isoxazol-3-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 2-[4-(3-cyano-4-pyrrolidin-1-yl-phenyl)-pyrimidin-2-ylamino]-oxazole-4-carboxylic acid amide; 5-[4-(3-cyano-4-pyrrolidin-1-yl-phenyl)-pyrimidin-2-ylamino]-2-methyl-2H-pyrazole-3-carboxylic acid amide; 5-[2-(5-methyl-thiazol-2-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(oxazol-2-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(4-methyl-thiazol-2-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 4-[4-(3-cyano-4-pyrrolidin-1-yl-phenyl)-pyrimidin-2-ylamino]-3-methyl-benzamide; 5-[2-(3-fluoro-phenylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(4-fluoro-phenylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(3-methoxy-phenylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(pyridin-3-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(3-methyl-isoxazol-5-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; 5-[2-(2-methyl-2H-pyrazol-3-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile; and 5-[2-(1-methyl-1H-pyrazol-3-ylamino)-pyrimidin-4-yl]-2-pyrrolidin-1-yl-benzonitrile. United States Patent No. 8,962,602 to Fernandez Rodriguez et al. discloses the use of unsaturated steroidal lactone derivatives related to bufadienolides. United States Patent No. 8,961,970 to Huang et al. discloses the use of combinations with the MEK inhibitor 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethyoxy)-amide and an antibody that is an IGFR1 inhibitor. United States Patent No. 8,952,151 to Chen et al. discloses the use of substituted amidopyridine or amidopyridazine derivatives that are histone demethylase inhibitors. United States Patent No. 8,951,993 to Hu et al. discloses the use of phosphorus-substituted aryl compounds as ALK or c-Met kinase inhibitors, including 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(4-dimethylphosphorylphenyl)pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-[1-[1-(dimethylphosphorylmethyl)-4-piperidyl]pyrazol-4-yl]pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-[1-(dimethylphosphorylmethyl)pyrazol-4-yl]pyridin-2-amine; 5-[4-

[(bis(dimethylphosphorylmethyl)amino)methyl]phenyl]-3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-[4-[(dimethylphosphorylmethylamino)methyl]phenyl]pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(5-dimethylphosphoryl-3-pyridyl)pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-[4-(dimethylphosphoryloxymethyl)phenyl]pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(4-dimethylphosphoryl-2-methoxy-phenyl)pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(4-dimethylphosphoryl-1-naphthyl)pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(4-dimethylphosphoryl-2-fluoro-5-methoxy-phenyl)pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(4-dimethylphosphorylphenyl)pyrazin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(4-dimethylphosphoryl-3-methoxy-phenyl)pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(4-dimethylphosphoryl-2-fluoro-phenyl)pyridin-2-amine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-(4-dimethylphosphoryl-3-fluoro-phenyl)pyridin-2-amine; and 3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-[4-dimethylphosphoryl-2-(trifluoromethyl)phenyl]pyridin-2-amine. United States Patent No. 8,946,444 to Lennox et al. discloses the use of tetrahydrocarbazoles as VEGF synthesis inhibitors. United States Patent No. 8,946,296 to Ortega Munoz et al. discloses the use of substituted heteroaryl- and aryl-cyclopropylamine acetamides as lysine specific demethylase-1 inhibitors, including 2-((*t*)-2-(4-(4-cyanobenzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-(3-cyanobenzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-(benzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-(4(benzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-(3-fluorobenzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-(3-chlorobenzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-(4-chlorobenzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-(3-brornobenzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-(3,5-difluorobenzyloxy)phenyl)cyclopropylamino)acetamide; 2-((*t*)-2-(4-phenethoxyphenyl)cyclopropylarnino)acetamide; 2-((*t*)-2-(3′-(trifluoromethyl)biphenyl-4-yl)cyclopropylamino)acetamide; 2-((*t*)-2-(3′-chlorobiphenyl-4-yl)cyclopropylamino)acetamide; 2-((*t*)-2-(6-(4-chlorophenyl)pyridin-3-

yl)cyclopropylamino)acetamide; (R)-2-((*t*)-2-(4-(3-fluorobenzyloxy)phenyl)cyclopropylamino)propanamide; (S)-2-((*t*)-2-(4-(4-fluorobenzyloxy)phenacyclopropylamino)propanamide; (R)-2-((*t*)-2-(4-(4-fluorobenzyloxy)phenyl)cyclopropylamino)propanamide; (S)-2-((*t*)-2-(4-(4-fluorobenzyloxy)phenyl)cyclopropylamino)propanamide; and (R)-2-((*t*)-2-(4-(benzyloxy)phenyl)cyclopropylamino)propanamide. United States Patent No. 8,946,246 to Magedov et al. discloses the use of rigidin analogs. United States Patent No. 8,946,235 to Butterworth et al. discloses the use of 2-(2,4,5-substituted-anilino)pyrimidine compounds as inhibitors of mutated EGFR. United States Patent No. 8,946,213 to Crawford et al. discloses the use of alkylated piperazines as Btk inhibitors including (S)-2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1(2H)-one; (S)-5-[5-fluoro-2-(hydroxymethyl)-3(1-methyl-5-(5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-8-thia-4,5-diazatricyclo[7.4.0.02,7]trideca-[(9),2(7),3-trien-6-one; (2S)-10-[5-fluoro-2-(hydroxymethyl)-3-[1-methyl-5-({5-[2-methyl-4-(oxetan-3-yl)piperazin-1-yl]pyridine-2-yl}amino)-6-oxo-1,6-dihydropyridin-3-yl]phenyl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.02,6]dodeca-2(6),7-dien-9-one; 2-(3-(5-(5-((2S,5R)-2,5-dimethyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one; (S)-2-(3-(5-(5-(2-ethyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one; (S)-2-(5-fluoro-2-(hydroxymethyl)-3-(1-methyl-5-(5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one; (S)-2-(3-(5-(5-(3,4-dimethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one; (R)-2-(3-(5-(5-(3,4-dimethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-c]indol-1(2H)-one; and (R)-2-(3-(5-(5-(2,4-dimethylpiperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-

-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one. United States Patent No. 8,937,095 to Zahn et al. discloses the use of dual Aurora kinase/MEK inhibitors including 3-[3-[[4-(dimethyloxidoaminomethy)anilino]-phenylmethylidene]-2-oxo-1H-indol-6-yl]-N-ethylprop-2-ynamide. United States Patent Application Publication No. 2015/0087664 by Blake et al. discloses the use of quinazolines as serine/threonine kinase inhibitors, including N-((4-chloro-3-fluorophenyl)(1-methyl-1H-pyrazol-4-yl)methyl)-2-((S)-1-hydroxypropan-2-ylamino)quinazoline-7-carboxamide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(4-chloro-3-fluoro-phenyl)-(1-methyl-1H-pyrazol-4-yl)-methyl]-amide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(S)-(3-fluoro-4-trifluoromethyl-phenyl)-(S)-pyrrolidin-2-yl-methyl]-amide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(4-chloro-3-fluoro-phenyl)-(1-methyl-1H-pyrazol-3-yl)-methyl]-amide; 2-isopropylamino-quinazoline-7-carboxylic acid [(S)-(3-fluoro-4-trifluoromethyl-phenyl)-(R)-pyrrolidin-2-yl-methyl]-amide; N-((4-chloro-3-fluorophenyl)(1-methyl-1H-pyrazol-3-yl)methyl)-2-((S)-1-hydroxypropan-2-ylamino)quinazoline-7-carboxamide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(S)-(3-fluoro-4-trifluoromethyl-phenyl)-(R)-pyrrolidin-2-yl-methyl]-amide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(R)-(3-chloro-4-fluoro-phenyl)-(R)-pyrrolidin-3-yl-methyl]-amide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(R)-(3-chloro-4-fluoro-phenyl)-(S)-pyrrolidin-3-yl-methyl]-amide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(S)-(3-chloro-4-fluoro-phenyl)-(S)-pyrrolidin-3-yl-methyl]-amide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(S)-(3-chloro-4-fluoro-phenyl)-(R)-pyrrolidin-3-yl-methyl]-amide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(S)-(4-chloro-3-fluoro-phenyl)-(1-methyl-1H-pyrazol-4-yl)-methyl]-amide; 2-(tetrahydropyran-4-ylamino)-quinazoline-7-carboxylic acid [(R)-(4-chloro-3-fluoro-phenyl)-(1-methyl-1H-pyrazol-4-yl)-methyl]-amide; and 2-((S)-2-hydroxy-1-methyl-ethylamino)-quinazoline-7-carboxylic acid. United States Patent Application Publication No. 2015/0087630 by Chen et al. discloses the use of diazacarbazoles. United States Patent Application Publication No. 2015/0087628 by Ostrem et al. discloses the use of modulators of K-Ras activity that include a Switch-2 binding pocket moiety and an electrophilic chemical moiety capable of forming a covalent bond with a

K-Ras cysteine residue or a K-Ras aspartate residue. United States Patent Application Publication No. 2015/0087600 by Popovici-Muller et al. discloses the use of inhibitors of mutants of isocitrate dehydrogenase 1 or isocitrate dehydrogenase 2. United States Patent Application Publication No. 2015/0086551 by Chen et al. discloses the use of hydroxamic acid derivatives that inhibit the HDAC pathway. United States Patent Application Publication No. 2015/0080392 by Wang et al. discloses the use of quinazoline derivatives as kinase inhibitors including one or more of EGFR, VEGFR-2, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFR, c-src, lck, Zap70 and fyn kinases, such as N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((4-hydroxybutyl)amino)methyl-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((3-phenylpropyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((n-hexylamino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((ethylamino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((N,N-diethyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-butenyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((2-(1,3-dihydroxypropyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-((5-((cyclohexylmethyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-(3-cyclohexenyl)ethyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((((3-chlorocyclohexyl)methyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((4-methoxybutyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((3-chlorobenzyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-(4-nitrophenyl)ethyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-(4-hydroxyphenyl)ethyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-(3,5-dimethoxyphenyl)ethylamino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-(3-hydroxy-5-fluorophenyl)ethyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-

fluorobenzyl)oxy)phenyl)-6-(5-(((2-(3-chloro-5-fluorophenyl)ethyl)amino)methyl)-2-furyl)-4-quinazolinamine; N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-,6-dihydroxyhexyl)amino)methyl)-2-furyl)-4-quinazolinamine; and N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-((bis(2-hydroxyethyl)amino)methyl)-2-furyl)-4-quinazolinamine. United States Patent Application Publication No. 2015/0079081 by Dotson et al. discloses the use of tricyclic PI3K inhibitors such as 1-[4-(3a,8-dimethyl-7-morpholin-4-yl-3,3a,8,8a-tetrahydro-2H-1-oxa-4,6,8-triaza-cyclopenta[a]inden-5-yl)-phenyl]-3-ethyl-urea; 5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)-4-methylpyrimidin-2-amine; 5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine; 5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)-4-(trifluoromethyl)pyridyl-2-amine; 5-(4-morpholino-8,9-dihydro-7H-[1,3]oxazino[2,3-e]purin-2-yl)pyrimidin-2-amine; 5-(4-morpholino-6,7,8,9-tetrahydropyrido[2,1-e]purin-2-yl)pyrimidin-2-amine; 5-(4-morpholino-6,7,8,9-tetrahydropyrido[2,1-e]purin-2-yl)pyridin-2-amine; 5-(4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)-4-(trifluoromethyl)pyridyl-2-amine; 5-(4-morpholino-7,8-dihydro-6H-pyrrolo[2,1-e]purin-2-yl)pyrimidin-2-amine; 6,6-dimethyl-4-morpholino-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purine; 5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyridin-2-amine; 5-(4-morpholino-8,9-dihydrospiro[[1,3]oxazino[2,3-e]purine-7,1′-cyclopropane]-2-yl)pyrimidin-2-amine; 5-(4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine; 5-(4-morpholino-8,9-dihydrospiro[[1,4]oxazino[3,4-e]purine-6,3′-oxetane]-2-yl)pyrimidin-2-amine; 5-(7,7-dimethyl-4-morpholino-8,9-dihydro-7H-[1,3]oxazino[2,3-e]purin-2-yl)pyrimidin-2-amine; 5-(4-morpholino-6-(trifluoromethyl)-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyridin-2-amine; and 5-(6,6-(hexadeuterio)dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine. United States Patent Application Publication No. 2015/0073054 by Strongin et al. discloses the use of furin inhibitors and inhibitors of other pro-protein convertases. United States Patent Application Publication No. 2015/0073003 by Dagan et al. discloses the use of sphingolipid analogs. United States Patent Application Publication No. 2015/065526 by Deng et al. discloses the use of Stat3 inhibitors including niclosamide. United States Patent Application Publication No. 2015/0057309

by Vakkalanka et al. discloses the use of 3,5-disubstituted-3h-imidazo[4,5-b]pyridine and 3,5-disubstituted-3H-[1,2,3]triazolo[4,5-b]pyridine compounds as c-Met modulators, including N-(2-amino-2-oxoethyl)-4-(3-(quinolin-7-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide: N-(2-(methylamino)-2-oxoethyl)-4-(3-(quinolin-6-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide: N-(3-amino-3-oxopropyl)-4-(3-(quinolin-6-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide: N-(3-(methylamino)-3-oxopropyl)-4-(3-(quinolin-6-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide 2-chloro-N-(2-(pyrrolidin-1-yl)ethyl)-4-(3-(quinolin-7-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide: 2-chloro-N-(2-hydroxyethoxy)-4-(3-(quinolin-6-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide: 2-chloro-N-(2-hydroxyethoxy)-4-(3-(quinolin-6-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide hydrochloride: 2-chloro-N-(2-hydroxyethoxy)-4-(3-(quinolin-6-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide 4-methylbenzenesulfonate 2-chloro-N-(2-hydroxyethoxy)-4-(3-(quinolin-6-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzamide hydrobromide; and sodium (2-chloro-4-(3-(quinolin-6-ylmethyl)-3H-[1,2,3]-triazolo[4,5-b]pyridin-5-yl)benzoyl)(2-hydroxyethoxy)amide. United States Patent Application Publication No. 2015/0057295 by Reiser et al. discloses the use of 6-alkynylpyridine derivatives as SMAC mimetics. United States Patent Application Publication No. 2015/0057293 by Angibaud et al. discloses the use of naphthyridine derivatives. United States Patent Application Publication No. 2015/0057286 by Reiser et al. discloses the use of bis-amidopyridines as SMAC mimetics. United States Patent Application Publication No. 2015/0051209 by Bock et al. discloses the use of MEK inhibitors with imidazoquinolone or imidazoquinoline moieties including 1-((3S,4S)-4-(8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)-3-fluoropiperidin-1-yl)-2-hydroxyethanone; 1-((3R,4R)-4-(8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)-3-fluoropiperidin-1-yl)-2-hydroxyethanone; 8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-1-(1-(2-methoxyethyl)piperidin-4-yl)-2-methyl-1H-imidazo[4,5-c]quinolone; 2-(4-(8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)piperidin-1-yl)ethanol; 8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1-(1-((3-methyloxetan-3-yl)methyl)piperidin-4-yl)-1H-imidazo[4,5-c]quinolone; 8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-

methyl-1-(1-(methylsulfonyl)piperidin-4-yl)-1H-imidazo[4,5-c]quinolone; 1-(4-(8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)piperidin-1-yl)-2-hydroxypropan-1-one; 1-(4-(8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)piperidin-1-yl)propan-2-ol; 8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-1-(1-(cyclopropylsulfonyl)piperidin-4-yl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolone; 8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-1-(1-(isopropylsulfonyl)piperidin-4-yl)-2-methyl-1H-imidazo[4,5-c]quinolone; 4-(8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)-N,N-dimethylpiperidine-1-sulfonamide; 4-(8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)-N,N-dimethylpiperidine-1-carboxamide; and 1-(4-(8-(2-chloro-4-(pyrimidin-2-yloxy)phenyl)-7-fluoro-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)piperidin-1-yl)ethanone. United States Patent Application Publication No. 2015/0045386 by Bencherif et al. discloses the use of (2S,3R)-N-(2-((3-pyridinyl)methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide. United States Patent Application Publication No. 2015/0045324 by Cha et al. discloses the use of fused pyrimidine derivatives, including N-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide; N-(3-((2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide; N-(3-((2-((4-morpholinophenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide; N-(3-((2-((4-((dimethylamino)methyl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide; N-(3-((2-((4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide; N-(3-((2-((3-fluoro-4-(1-methylpiperazin-4-yl)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide; N-(3-((2-((4-(2-dimethylamino)ethyl)amino)-3-fluorophenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide; N-(3-((2-((3-fluoro-4-((1-methylpiperidin-4-yl)amino)phenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide; N-(3-(2-(3-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino)-furo[3,2-d]pyrimidin-4-yloxy)-phenyl)-acrylamide; and N-(3-((2-((4-sulfamoylphenyl)amino)furo[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide. United States Patent Application Publication No. 2015/0038506 by Nacro et al. discloses the use of imidazopyrazine, imidazopyridine, imidazopyridazine and imidazpyrimidine compounds

as MNK1 or MNK2 inhibitors. United States Patent Application Publication No. 2015/0038430 by Nash et al. discloses the use of peptidomimetic macrocycles binding to MCL-1. United States Patent Application Publication No. 2015/0031669 by Woodhead et al. discloses the use of benzopyrazines as inhibitors of FGFR kinases. United States Patent Application Publication No. 2015/0011561 by Allwein et al. discloses the use of fused bicyclic 2,4-diaminopyridine derivatives as dual ALK and FAK inhibitors. United States Patent Application Publication No. 2015/0011506 by Olhava et al. discloses the use of boron-containing proteasome inhibitors such as [(1R)-1-({[(2,3-difluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(5-chloro-2-fluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(3,5-difluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2,5-difluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2-bromobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2-fluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2-chloro-5-fluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(4-fluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(3,4-difluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(3-chlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(3,4-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(3-fluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2-chloro-4-fluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2,3-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2-chlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2,4-difluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(4-chloro-2-fluorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(4-chlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; [(1R)-1-({[(2,4-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid; and [(1R)-1-({[(3,5-dichlorobenzoyl)amino]acetyl}amino)-3-methylbutyl]boronic acid. United States Patent Application Publication No. 2015/0011461 by Crawford et al. discloses the use of heteroaryl pyridone and aza-pyridone amide compounds as Btk inhibitors, including N-

[5-[2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-3-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-2-oxo-3-pyridyl]cyclobutanecarboxamide; N-[5-[2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-3-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-2-oxo-3-pyridyl]cyclopropanecarboxamide; 2-cyclopropyl-N-[5-[2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-3-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-2-oxo-3-pyridyl]acetamide; N-[5-[2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-3-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-2-oxo-3-pyridyl]oxetane-3-carboxamide; N-[5-[2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-3-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-2-oxo-3-pyridyl]-2-morpholino-acetamide; N-[5-[2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-3-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-2-oxo-3-pyridyl]-2-methyl-cyclopropanecarboxamide; and N-[5-[2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-3-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-2-oxo-3-pyridyl]propanamide. United States Patent Application Publication No. 2015/0005309 by Barfacker et al. discloses the use of substituted imidazopyrazines as PI3K/Akt inhibitors, including 2-[4-(1-aminocyclobutyl)phenyl]-3-phenylimidazo[1,2-a]pyrazin-8-ol; 1-[4-(6,8-dimethyl-3-phenylimidazo[1,2-a]pyrazin-2-yl)phenyl]-cyclobutanamine; 1-[4-(6-bromo-8-methoxy-3-phenylimidazo[1,2-a]pyrazin-2-yl)phenyl]cyclobutanamine; 1-[4-(6-ethyl-8-methoxy-3-phenylimidazo[1,2-a]pyrazin-2-yl)phenyl]-cyclobutanamine; ethyl 2-[4-(1-aminocyclobutyl)phenyl]-3-phenylimidazo[1,2-a]pyrazine-6-carboxylate; 2-[4-(1-aminocyclobutyl)phenyl]-3-phenylimidazo[1,2-a]pyrazine-6-carboxamide; methyl 2-[4-(1-aminocyclobutyl)phenyl]-8-methoxy-3-phenylimidazo[1,2-a]-pyrazine-6-carboxylate; and 2-[4-(1-aminocyclobutyl)phenyl]-8-methoxy-3-phenylimidazo[1,2-a]pyrazine-6-carboxamide. United States Patent Application Publication No. 2014/0378466 by Maderna et al. discloses the use of derivatives of N-(arylamino) sulfonamides as MEK inhibitors. United States Patent Application Publication No. 2014/0371254 by Leung et al. discloses the use of isoquinoline alkaloids including sanguinarine. United States Patent Application Publication No. 2014/0371158 by Chadli et al. discloses the use of beauvericin and analogs and derivatives as Hsp90 chaperone pathway inhibitors. United States Patent

Application Publication No. 2014/0357605 by Gavai et al. discloses the use of bis-(fluoroalkyl)-1,4-benzodiazapinone compounds as Notch receptor inhibitors, including (2R,3S)--N-((3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide; (2R,3S)-N-((3S)-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide; (2R,3S)-N-((3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2-(2,2,2-trifluoroethyl)-3-(3,3,3-trifluoropropyl)succinamide; (2R,3S)-N-((3S)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(2,2,2-trifluoroethyl)-2-(3,3,3-trifluoropropyl)succinamide; (2R,3S)-N-((3S)-1-($2H_3$)methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide; (2R,3S)-N-((3S)-7-chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide; (2R,3S)-N-((3S)-8-methoxy-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide; (2R,3S)-N-((3S)-8-fluoro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide; and (2R,3S)-N-((3S)-7-methoxy-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinamide. United States Patent Application Publication No. 2014/0357594 by Hendrickson et al. discloses the use of purinyl-containing heteroaryl compounds that inhibit DNA methyltransferase. United States Patent Application Publication No. 2014/0350096 by Yang et al. discloses the use of antrocin.

[0099] Additional agents that possess anti-neoplastic activity against ovarian cancer are known in the art. These additional agents can be included in drug combinations according to the present invention in a therapeutically effective quantity together with a therapeutically effective quantity of a substituted hexitol derivative as described above. One or more than one of these additional agents can be used. These additional agents can be used together with one or more of the agents as described above for activity against ovarian cancer in drug combinations including a substituted hexitol derivative such as dianhydrogalactitol or diacetyldianhydrogalactitol. Collectively, these agents are referred to herein as “Additional Secondary Agents with Activity Against Ovarian Cancer.” These agents include the following: United States Patent No. 8,981,131 to Bhedi et al., discloses the use of tricyclic compounds such as

(5aR,9bS)-3a-hydroxy-5a,9-dimethyl-3-((4-methylpiperazin-1-yl)methyl)-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-b]furan-2(9bH)-one hydrochloride; ethyl 4-(((5aR,9bS)-3a-hydroxy-5a,9-dimethyl-2-oxo-2,3,3a,4,5,5a,6,7,8,9b-decahydronaphtha[1,2-b]furan-3-yl)methyl)piperazine-1-carboxylate hydrochloride; (5aR,9bS)-3a-hydroxy-5a,9-dimethyl-3-((4-o-tolylpiperazin-1-yl)methyl)-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-b]furan-2(9bH)-one hydrochloride; or (5aR,9bR)-3a-hydroxy-3-((((5aR,9bS)-3a-hydroxy-5a,9-dimethyl-2-oxo-2,3,3a,4,5,5a,6,7,8,9b-decahydronaphtho[1,2-b]furan-3-yl)methylamino)methyl)-5a,9-dimethyl-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-b]furan-2(9bH)-one hydrochloride). United States Patent No. 8,981,094 to Bongartz et al. discloses the use of piperidine/piperazine derivatives that are DGAT inhibitors, particularly DGAT1 inhibitors. United States Patent No. 8,981,085 to Le Huerou et al. discloses the use of pyrrolopyrimidine CHK1 or CHK2 inhibitors. United States Patent No. 8,981,084 to Balogu et al. discloses the use of oxadiazole HDAC inhibitors. United States Patent No. 8,980,955 to Turchi et al. discloses the use of inhibitors of Replication Protein A that are haloester isoborneol derivatives. United States Patent No. 8,980,934 to Pauls et al. discloses the use of indazole inhibitors of TTK protein kinase. United States Patent No. 8,980,933 to Schobert et al. discloses the use of combretastatin analogs. United States Patent No. 8,980,909 to Chen et al. discloses the use of HDAC inhibiting derivatives of camptothecin. United States Patent No. 8,980,902 to Brown et al. discloses the use of piperazinylbenzamide PARP inhibitors. United States Patent No. 8,980,879 to Liu et al. discloses the use of BET bromodomain inhibitors including 5-(cyclopropylmethyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; 5-(4-fluorophenyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; 5-(2,4-difluorophenyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; 5-(cyclopropanecarbonyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; 5-(4-fluorophenyl)-4-(2-methoxyethyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; methyl 3-(5-(4-fluorophenyl)-11-methyl-8-((methylsulfonyl)methyl)-1-oxo-2,4,5,11-tetrahydro-1H-2,5,11-

triazadibenzo[cd,h]azulen-4-yl)propanoate; N-(5-(4-fluorophenyl)-11-methyl-1-oxo-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-8-yl)ethanesulfonamide; 8-fluoro-5-(4-fluorophenyl)-11-methyl-2,4,5,11-tetrahydro-1H-2,5,6,11-tetraazadibenzo[cd,h]azulen-1-one; N-(5-(4-fluorophenyl)-11-methyl-1-oxo-2,4,5,11-tetrahydro-1H-2,5,6,11-tetraazadibenzo[cd,h]azulen-8-yl)-2-(1-methyl-1H-pyrazol-4-yl)acetamide; 8-amino-5-(4-fluorophenyl)-11-methyl-2,4,5,11-tetrahydro-1H-2,5,11-triaza- dibenzo[cd,h]azulen-1-one; N-(5-(4-fluorophenyl)-11-methyl-1-oxo-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-8-yl)benzenesulfonamide; N-(4-(N-(5-(4-fluorophenyl)-11-methyl-1-oxo-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-8-yl)sulfamoyl)phenyl)acetamide. United States Patent No. 8,980,875 to Mailliet et al. discloses the use of platinum N-heterocyclic carbene derivatives. United States Patent No. 8,980,850 to Smith discloses the use of NEDD8-activating enzyme inhibitors such as ((1S,2S,4R)-4-(4-((1S)-2,3-dihydro-1H-inden-1-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxycyclopentyl)methyl sulfamate or {(1S,2S,4R)-4-[(6-{[(1R,2S)-5-chloro-2-methoxy-2,3-dihydro-1H-inden-1-yl]amino}pyrimidin-4-yl)oxy]-2-hydroxycyclopentyl}methyl sulfamate. United States Patent No. 8,980,838 to Wang et al. discloses the use of cyclic peptidomimetic inhibitors of the WDR5/MLL1 interaction. United States Patent No. 8,980,268 to Lowy et al. discloses the use of anti-Ang-2 antibodies. United States Patent No. 8,980,257 to Kaneda et al. discloses the use of anti-TGFα antibodies. United States Patent No. 8,975,398 to Hansen et al. discloses the use of NAMPT inhibitors such as N-{4-[1-(2-methylpropanoyl)piperidin-4-yl]phenyl})-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(2-chlorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-[4-({1-[(2S)-2-methylbutanoyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(1,3-thiazol-2-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(tetrahydro-2H-pyran-4-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; N-[4-({1-[difluoro(phenyl)acetyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-[4-({1-[(4,4-difluorocyclohexyl)carbonyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(2-methyl-2-phenylpropanoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide;

1-(pyridazin-3-yl)-N-(4-{[1-(1,3-thiazol-4-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; N-[4-({1-[(5-methylthiophen-2-yl)carbonyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-{4-[(1-{[4-(trifluoromethyl)phenyl]acetyl}piperidin-4-yl)oxy]phenyl}azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-[4-({1-[3-(trifluoromethyl)benzoyl]piperidin-4-yl}oxy)phenyl]azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(thiophen-3-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-[4-({1-[3-(trifluoromethoxy)benzoyl]piperidin-4-yl}oxy)phenyl]azetidine-3-carboxamide; N-(4-{[1-(3-methylbutanoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(tetrahydrofuran-3-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; N-[4-({1-[(3-fluorophenyl)acetyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(2-fluorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(2,4-difluorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(4-fluorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; and N-(4-{[1-(3-fluorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide.

United States Patent No. 8,975,376 to Blein et al. discloses the use of anti-α_2-integrin antibodies. United States Patent No. 8,975,287 to Karp et al. discloses the use of 1,2,4-oxadiazole benzoic acid compounds. United States Patent No. 8,975,267 to Caldarelli et al. discloses the use of tricylic pyrrole derivatives such as N-(2,6-diethylphenyl)-9-(methoxymethyl)-2-{[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}-8-methyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, 2-[(4-bromo-2-methoxyphenyl)amino]-N-(2,6-diethylphenyl)-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, N-(2,6-diethylphenyl)-2-({2-methoxy-4-[4-(pyrrolidin-1-yl)piperidin-1-yl]phenyl}amino)-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, N-(2,6-diethylphenyl)-2-({4-[4-(dimethylamino)piperidin-1-yl]-2-methoxyphenyl}amino)-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, N-(2,6-diethylphenyl)-2-{[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide,

N-(2,6-diethylphenyl)-2-({4-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methoxyphenyl}amino)-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, 2-{[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, and 2-[(4-bromo-2-methoxyphenyl)amino]-N-(2,6-diethylphenyl)-9-methyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide. United States Patent No. 8,974,781 to Bauer et al. discloses the use of anti-P-cadherin antibodies. United States Patent No. 8,969,587 to Abraham et al. discloses the use of BRAF kinase inhibitors, such as 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea. United States Patent No. 8,969,401 to Maier et al. discloses the use of sulfonylpyrroles as HDAC inhibitors. United States Patent No. 8,969,396 to Du et al. discloses the use of BRAF inhibitors including Hsp90 inhibitors such as 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole. United States Patent No. 8,969,395 to Ribeiro Salvador et al. discloses the use of triterpenoid derivatives. United States Patent No. 8,969,381 to Wilson et al. discloses the use of chemokine CXCR4 modulators such as N^1-(((S)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine; N^1-(((R)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine; N^1-(((S)-4-benzylpiperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine; and N^1-(((R)-4-benzylpiperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine. United States Patent No. 8,969,379 to Furitsu et al. discloses the use of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide. United States Patent No. 8,969,375 to Lai et al. discloses the use of CDK9 kinase inhibitors such as 4-[1-(3-fluorobenzyl)-2,3-dihydro-1H-indol-6-yl]-2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine; 1-(3-fluorobenzyl)-6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-benzimidazole; 1-benzyl-6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-indole-3-carbonitrile; 1-(3-fluorobenzyl)-6-{2-[1-(methylsulfonyl)piperidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-1H-benzimidazole; 6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole; 6-{2-[1-(methylsulfonyl)piperidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole; 5-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-3-(tetrahydro-2H-pyran-4-ylmethyl)-

3H-imidazo[4,5-b]pyridine; 1-(3-fluorobenzyl)-6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-indole-3-carbonitrile; 4-[5-fluoro-1-(3-fluorobenzyl)-1H-indol-6-yl]-2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine; 6-{2-[1-(2,3-dihydroxypropyl)piperidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-1-(3-fluorobenzyl)-1H-indole-3-carbonitrile; 1-(3-fluorobenzyl)-6-{2-[1-(methylsulfonyl)piperidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-1H-indole-3-carbonitrile; and 1-[(5-fluoropyridin-3-yl)methyl]-6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-benzimidazole. United States Patent No. 8,969,366 to Marchionni et al. discloses the use of substituted pyrimidinylpyrrolopyridinone derivatives. United States Patent No. 8,969,360 to Charrier et al. discloses the use of inhibitors of ATR kinase. United States Patent No. 8,969,335 to Hoelzemann et al. discloses the use of inhibitors of IKKε and TBK1 including benzonitrile derivatives. United States Patent No. 8,969,313 to Yu discloses the use of DACT protein activators. United States Patent No. 8,962,855 to Chen et al. discloses the use of nitrogen mustard derivatives. United States Patent No. 8,962,679 to Wang et al. discloses the use of daidzein derivatives including alkoxychromenon-4-ones. United States Patent No. 8,962,663 to Mahadevan et al. discloses the use of pleckstrin homology domain inhibitors. United States Patent No. 8,962,642 to Mortimore et al. discloses the use of 5-cyano-4-(pyrrolo [2,3-b] pyridine-3-yl)pyrimidine derivatives. United States Patent No. 8,962,637 to McAllister et al. discloses the use of substituted aromatic bicyclic compounds as c-SRC/JAK inhibitors. United States Patent No. 8,962,630 to Brain et al. discloses the use of pyrrolopyrimidine compounds including 7-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide as CDK protein kinase inhibitors. United States Patent No. 8,962,620 to Kuntz et al. discloses the use of substituted 6,5-fused bicyclic aryl compounds. United States Patent No. 8,962,619 to Ashwell et al. discloses the use of substituted imidazopyridinyl-aminopyridine compounds. United States Patent No. 8,962,611 to Christopher et al. discloses the use of substituted imidazopyridines as HDM2 inhibitors. United States Patent No. 8,962,608 to Brubaker et al. discloses the use of cycloalkylnitrile pyrazole carboxamides as janus kinase inhibitors. United States Patent No. 8,961,966 to Schoeberl et al. discloses the use of anti-ERBB3 antibodies. United States Patent No. 8,957,109 to Heaton et al. discloses the use of chroman derivatives. United States Patent No. 8,957,103 to

Dannhardt et al. discloses the use of conjugated 3-(indolyl)- and 3-(azaindolyl)-4-arylmaleimide compounds. United States Patent No. 8,957,102 to Kim et al. discloses the use of c-Met inhibitors including 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid [3-fluoro-4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)-phenyl]-amide; 2-(4-fluoro-phenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid [3-fluoro-4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)-phenyl]-am- ide; 2-(4-fluoro-phenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid [3-fluoro-4-(3-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)-phenyl]-amide; N-(3-fluoro-4-(2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide; and N-(3-fluoro-4-(2-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide. United States Patent No. 8,957,078 to Brenchley et al. discloses the use of pyrazolopyrimidines as ATR kinase inhibitors. United States Patent No. 8,957,068 to Caferro et al. discloses the use of 3-pyrimidin-4-yl-oxazolidin-2-ones as inhibitors of mutant IDH. United States Patent No. 8,957,056 to Danishefsky et al. discloses the use of migrastatin analogs. United States Patent No. 8,956,613 to Wu et al. discloses the use of gemcitabine prodrugs. United States Patent No. 8,952,163 to Blackburn discloses the use of substituted hydroxamic acids as HDAC6 inhibitors. United States Patent No. 8,952,161 to Beaton et al. discloses the use of gonadotrophin-releasing hormone receptor antagonists. United States Patent No. 8,952,157 to Ding et al. discloses the use of inhibitors of anti-apoptotic Bcl-2 proteins such as 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,3-difluorophenoxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 2-(4-amino-3-chlorophenoxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,5-dichlorophenoxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; N-(4-((4-aminotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrophenylsulfonyl)-2-(3-chlorophenoxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-

yl]methyl}piperazin-1-yl)-2-(3-fluorophenoxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 2-(2-chlorophenoxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 2-(2-chloro-4-fluorophenoxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2-fluorophenoxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2-fluorophenoxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-nitrophenyl}sulfonyl)benzamide; and 2-(3-chlorophenoxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide. United States Patent No. 8,952,054 to Kufe et al. discloses the use of small molecule inhibitors of MUC1 oligomerization such as flavone derivatives. United States Patent No. 8,952,043 to Blaquiere et al. discloses the use of benzoxepin PI3K inhibitors. United States Patent No. 8,951,987 to Hamilton et al. discloses the use of tetrahydrouridine derivatives. United States Patent No. 8,951,536 to Combs et al. discloses the use of N-hydroxyamidino heterocycles as modulators of indoleamine 2,3-dioxygenase. United States Patent No. 8,946,445 to Wang discloses the use of heterocyclic apoptosis inhibitors such as (Z)-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-4H-thieno[3,2-b]pyrrole (Z)-2-chloro-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-4H-thieno[3,2-b]pyrrole; (Z)-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-2-methyl-4H-thieno[3,2-b]pyrrole; (Z)-2-bromo-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-4H-thieno[3,2-b]pyrrole; (Z)-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-6H-thieno[2,3-b]pyrrole; and (Z)-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-2-methyl-6H-thieno[2,3-b]pyrrole. United States Patent No. 8,946,413 to Hughes et al. discloses the use of 3-aminocyclopentanecarboxamides as chemokine receptor antagonists. United States Patent No. 8,946,409 to Becker et al. discloses the use of polycyclic β-lactam derivatives. United States Patent No. 8,946,289 to Hong et al. discloses the use of

manassatin compounds that block the HIF pathway. United States Patent No. 8,946,278 to Seefeld et al. discloses the use of heterocyclic carboxamides as AKT inhibitors, such as N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1- -methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; and N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide. United States Patent No. 8,946,205 to Curd et al. discloses the use of hypoxia activated prodrugs, including N,N′-bis(2-bromoethyl)phosphorodamidic acid (1-methyl-2-nitro-1H-imidazol-5-yl)methyl ester. United States Patent No. 8,946,239 to Gangjee discloses the use of substituted pyrrolo-, furano-, and cyclopentylpyrimidine bicyclic compounds. United States Patent No. 8,946,235 to Butterworth et al. discloses the use of 2-(2,4,5-substituted-anilino)pyrimidine compounds. United States Patent No. 8,946,224 to Craighead et al. discloses the use of substituted [1,2,4]triazolo[4,3-a]pyrazines. United States Patent No. 8,946,216 to Deng et al. discloses the use of indazole derivatives as ERK inhibitors, including N-[3-[6-(1-methylethoxy)-3-pyridinyl]-1H-indazol-5-yl]-4-(phenylmethyl)-2-morpholinecarboxamide; N-[3-[6-(1-methylethoxy)-3-pyridinyl]-1H-indazol-5-yl]-2-morpholinecarboxamide; N-[3-(4-pyridinyl)-1H-indazol-5-yl]-4-(4-thiazolylmethyl)-2-

morpholinecarboxamide; N-[3-(4-pyridinyl)-1H-indazol-5-yl]-4-(3-thienylmethyl)-2-morpholinecarboxamide; 4-[(2-fluorophenyl)methyl]-N-[3-(4-pyridinyl)-1h-indazol-5-yl]-2-morpholinecarboxamide; N-[3-(4-pyridinyl)-1H-indazol-5-yl]-4-(2-pyridinylmethyl)-2-morpholinecarboxamide; N-[3-(4-pyridinyl)-1H-indazol-5-yl]-4-(2-pyridinylmethyl)-2-morpholinecarboxamide; and 4-[(2-bromophenyl)methyl]-N-[3-(4-pyridinyl)-1H-indazol-5-yl]-2-morpholinecarboxamide. United States Patent No. 8,940,936 to Lee et al. discloses the use of aryloxy phenoxy acrylic compounds. United States Patent No. 8,940,760 to Page et al. discloses the use of pyrazolopyridine derivatives as NADPH oxidase inhibitors. United States Patent No. 8,940,756 to Flynn et al. discloses the use of dihydronaphthyridines as c-Kit inhibitors. United States Patent No. 8,940,737 to Wang et al. discloses the use of apoptosis-inducing agents, such as 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-benzyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-(4-hydroxybenzyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-- [1-(1-phenylethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{4-[2-(dimethylamino)ethoxy]benzyl}-1H-pyrazol-4-yl)pyridine-2-carboxylic acid; 3-(1-benzyl-1H-pyrazol-4-yl)-6-{8-[(5,6-difluoro-1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[2-(4-fluorophenyl)ethyl]-1H-pyrazol-4-yl}pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-(3-chlorobenzyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; and 3-(1-benzyl-1H-pyrazol-4-yl)-6-{8-[(6-fluoro-1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}pyridine-2-carboxylic acid. United States Patent No. 8,940,733 to Howard et al. discloses the use of unsymmetrical pyrrolobenzodiazepine dimers. United States Patent No. 8,940,726 to Duncan et al. discloses the use of PRMT5 inhibitors. United States Patent No. 8,937,193 to Pellecchia et al. discloses the

use of apogossypolone derivatives. United States Patent No. 8,937,094 to Burlison et al. discloses the use of Hsp90 modulators, including 5-(4-ethoxy-2-hydroxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-methoxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-propoxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-isopropoxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2,4-dimethoxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-isopropylphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-methylphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(4-hydroxy-3-isopropylphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(3-tert-butyl-4-hydroxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide; and 5-(4-hydroxy-3-propylphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide. United States Patent No. 8,937,068 to Seipelt et al. discloses the use of pyridopyrazine compounds. United States Patent No. 8,933,212 to Fayard et al. discloses the use of protease nexin 1 inhibitors to reduce metastasis. United States Patent No. 8,933,116 to Wu et al. discloses the use of γ-secretase inhibitors. United States Patent No. 8,933,103 to Ohki et al. discloses the use of Axl inhibitors that are pyridone derivatives including N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride. United States Patent No. 8,933,084 to Andrews et al. discloses the use of macrocyclic compounds as Trk inhibitors such as (6R)-9-fluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione. United States Patent No. 8,933,080 to Singh et al. discloses the use of bridged bicyclic heteroaryl substituted triazoles as Axl inhibitors. United States Patent No. 8,933,053 to McGuigan et al. discloses the use of phosphoramidate derivatives of 5-fluoro-2′-deoxyuridine. United States Patent No. 8,927,718 to Sasaki et al. discloses the use of fused heterocyclic ring derivatives as Smo inhibitors, including 3,6-diethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide; 3-ethenyl-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide; and 6-Ethyl-3-(ethylamino)-N-[1-

(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide. United States Patent No. 8,927,717 to Huang et al. discloses the use of thiochromeno[2,3-c]quinolin-12-one derivatives including 3-((4-chlorophenyl)thio)-2-hydroxyquinoline-4-carboxylic acid, 6,9-dichloro-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-hydroxy-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-methoxy-12H-thiochromeno[2,3-c]quinolin-12-one 10-chloro-6-dimethylamino-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-(piperazin-1-yl)-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-(4-methylpiperazin-1-yl)-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-(4-ethylpiperazin-1-yl)-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-(4-(2-hydroxyethyl)piperazin-1-yl)-12H-thiochromeno[2,3-c]quinolin-12-one, and 6-(4-benzylpiperazin-1-yl)-10-chloro-12H-thiochromeno[2,3-c]quinolin-12-one. United States Patent No. 8,927,711 to Abraham et al. discloses the use of quinazoline JAK inhibitors, including (3-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone; (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(3-fluorophenyl)methanone; (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone; (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanone; (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(2-methoxyphenyl)methanone; (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanol; 2-(fluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)quinazolin-4-amine; 2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine; 2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)quinazolin-4-amine; N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(difluoro(4-fluorophenyl)methyl)quinazolin-4-amine; 3-(2-(4-fluorobenzoyl)quinazolin-4-ylamino)-1H-pyrazole-5-carbonitrile; (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanol; 2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine; 2-(amino(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine; 3-(2-((4-fluorophenyl)(hydroxy)methyl)quinazolin-4-ylamino)-1H-pyrazole-5-carbonitrile; (5-fluoro-4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanol; (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)-7-(trifluoromethyl)quinazolin-2-yl)methanone; and (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)-7-(trifluoromethyl)quinazolin-2-yl)methanol. United

States Patent No. 8,927,580 to Richardson et al. discloses the use of dipyridyl thiosemicarbazones such as di-2-pyridylketone 4-ethyl-4-methyl-3-thiosemicarbazone. United States Patent No. 8,927,562 to Meng et al. discloses the use of fused tricyclic inhibitors of mTOR. United States Patent No. 8,927,560 to Ahmed et al. discloses the use of 4-aza-2,3-didehydropodophyllotoxin compounds. United States Patent No. 8,927,548 to Ying et al. discloses the use of triazole compounds that are Hsp90 inhibitors. United States Patent No. 8,927,538 to Kamal et al. discloses the use of carbazole linked pyrrolo[2, 1-c][1,4]benzodiazepine hybrids as agents reacting with DNA to form an N2-guanine adduct that lies within the minor groove of duplex DNA via an acid-labile aminal bond to the electrophilic imine at the N10-C11 position. United States Patent No. 8,927,533 to Giannini et al. discloses the use of lactam-substituted thio derivatives. United States Patent No. 8,921,565 to Flynn et al. discloses the use of pyridone amides as c-Met kinase inhibitors, such as N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-(2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-pivalamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-isobutyramidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide. United States Patent No. 8,921,522 to Kamal et al. discloses the use of benzothiazole derivatives including olefins, chalcones, pyrazolines, pyrazole, isoxazolines, and isoxazoles linked to 2-phenylbenzothiazoles. United States Patent No. 8,921,546 to Chao discloses the use of imidazothiazoles such as 7-(2-morpholin-4-yl-ethoxy)-2-(4-nitro-phenyl)imidazo[2,1-b][1,3]benzothiazole and 4-(7-(2-morpholinoethoxy)benzo[d]imidazo[2,1-b]thiazol-2-yl)aniline. United States Patent No. 8,921,414 to Reddell et al. discloses the use of spiroketals. United States Patent No. 8,921,407 to Ying et al. discloses the use of pyrazole compounds as Hsp90 modulators. United States Patent No. 8,921,367 to Friberg et al. discloses the use of AMG 900 (N-(4-(3-(2-aminopyrimidin-4-yl)pyridin-2-yloxy)phenyl)-4-(4-methylthiophen-2-

yl)phthalazin-1-amine) as Aurora kinase inhibitor. United States Patent No. 8,920,799 to Graham et al. discloses the use of Axl ligand-binding portion of Axl tyrosine kinase receptor. United States Patent No. 8,778,340 to Dupont et al. discloses the use of anti-angiogenesis agents including antibodies. United States Patent No. 8,748,470 to Lengyel et al. discloses the use of fatty acid binding protein inhibitors including carbazole butanoic acids, aryl sulfonamides, sulfonylthiophenes, 4-hydroxypyrimidines, 2,3-dimethylindoles, benzoylbenzenes, biphenyl-alkanoic acids, 2-oxazole-alkanoic acids, tetrahydropyrimidones, pyridones, pyrazinones, aryl carboxylic acids, tetrazoles, triazolopyrimidinones, indoles, BMS480404 ((2S)-2-[2,3-bis[(2-chlorophenyl)methoxy]phenyl]-2-hydroxyacetic acid), or BMS309403 (2-[[2'-(5-ethyl-3,4-diphenyl-1*H*-pyrazol-1-yl)[1,1'-biphenyl]-3-yl]oxy]-acetic acid. United States Patent No. 8,541,433 to Clozel et al. discloses the use of macitentan. United States Patent No. 8,362,072 to Jensen et al. discloses the use of BRCA1 production enhancers. United States Patent No. 8,268,889 to Kloog et al. discloses the use of farnesylthiosalicylic acid and analogs. United States Patent No. 7,968,514 to Coelingh Bennink et al. discloses the use of immunogenic peptides. United States Patent No. 7,323,164 to Chandrasekher et al. discloses the use of interleukin 24. United States Patent No. 7,074,575 to Chandrasekher et al. discloses the use of interleukin 19. United States Patent No. 6,237,307 to Miller et al. discloses the use of 2-phenyl-1-[4-(2-aminoethoxy)-benzyl]-indole derivatives. United States Patent No. 5,597,798 to Howell et al. discloses the use of combinations with taxol and epidermal growth factor. United States Patent Application Publication No. 2014/0336150 by Frederick discloses the use of karenitecin (7-[(2′-trimethylsilyl)ethyl]-20(S) camptothecin). United States Patent Application Publication No. 2014/0315959 by Moore et al. discloses the use of benzylidinebenzohydrazides. United States Patent Application Publication No. 2014/0309184 by Rocconi et al. discloses the use of Smo inhibitors used in combination with other drugs, including platinum-containing agents. United States Patent Application Publication No. 2014/0302174 by Chan et al. discloses combination therapy with gemcitabine, cisplatin or carboplatin, and 5-[2-tert-butyl-5-(4-fluoro-phenyl)-1H-imidazol-4-yl]-3-(2,2-dimethyl-propyl)-3H-imidazo[4,5-b]pyridin-2-ylamine. United States Patent Application Publication No. 2014/0275174 by Moore et al. discloses the use of 2-

amino-4H-naphtho[1,2-b]pyran-3-carbonitriles. United States Patent Application Publication No. 2014/0134169 by Kuhnert et al. discloses the use of Dll4 antagonists. United States Patent Application Publication No. 2013/0231286 by Chen discloses the use of prolactin receptor antagonist. United States Patent Application Publication No. 2013/0203861 by Liu et al. discloses the use of cyclohexenone compounds. United States Patent Application Publication No. 2012/0269827 by Whiteman et al. discloses the use of conjugates with CD56. United States Patent Application Publication No. 2012/0237502 by Darnowski discloses the use of 17,20-lyase inhibitors such as 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene, 6-[(7S)-7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl]-N-methyl-2-naphthalenecarboxamide, 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene, or 6-[(7S)-7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl]-N-methyl-2-naphthalenecarboxamide. United States Patent Application Publication No. 2012/0183546 by Weinreich discloses the use of angiopoietin-2 inhibitor. United States Patent Application Publication No. 2010/0009330 by Sherman et al. discloses the use of PARP inhibitors including 4-iodo-3-nitrobenzamide. United States Patent Application Publication No. 2009/0118271 by Umeda et al. discloses the use of water-soluble prodrugs such as (9S)-1-butyl-9-ethyl-9-hydroxy-1H,12H-pyrano[3′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-9-ethyl-9-hydroxy-1-[2-(4-morpholino)ethyl]-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-1-[3-(dimethylamino)propyl]-9-ethyl-9-hydroxy-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-9-ethyl-9-hydroxy-1-phenethyl-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-9-ethyl-9-hydroxy-1-[2-(pyridin-2-yl)ethyl]-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-9-ethyl-1-heptyl-9-hydroxy-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; and (9S)-9-ethyl-9-hydroxy-1-propyl-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-

trione. United States Patent Application Publication No. 2009/0099102 by Ye et al. discloses the use of ginkgolides, including ginkgolides A and B. United States Patent Application Publication No. 2007/0299020 by Zeldis discloses the use of 4-(amino)-2(2,6-dioxo(3-piperidyl)-isoindoline-1,3-dione. United States Patent Application Publication No. 2006/0058217 by White et al. discloses the use of antialamin. United States Patent Application No. 2005/0272766 by Koya et al. discloses the use of 1-glyoxylamide indolizines.

[0100] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by exploiting the substituted hexitol derivative such as dianhydrogalactitol as a chemosensitizer where no measureable activity is observed when used alone but in combination with other therapeutics a more than additive or synergistic improvement in efficacy is observed. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: as a chemosensitizer in combination with topoisomerase inhibitors; as a chemosensitizer in combination with fraudulent nucleosides; as a chemosensitizer in combination with fraudulent nucleotides; as a chemosensitizer in combination with thymidylate synthetase inhibitors; as a chemosensitizer in combination with signal transduction inhibitors; as a chemosensitizer in combination with cisplatin, oxaliplatin, or other platinum analogs; as a chemosensitizer in combination with alkylating agents such as BCNU, BCNU wafers, Gliadel, CCNU, bendamustine (Treanda), or Temozolomide (Temodar); as a chemosensitizer in combination with anti-tubulin agents; as a chemosensitizer in combination with antimetabolites; as a chemosensitizer in combination with berberine; as a chemosensitizer in combination with apigenin; as a chemosensitizer in combination with amonafide; as a chemosensitizer in combination with colchicine or analogs; as a chemosensitizer in combination with genistein; as a chemosensitizer in combination with etoposide; as a chemosensitizer in combination with cytarabine; as a chemosensitizer in combination with camptothecins; as a chemosensitizer in combination with vinca alkaloids; as a chemosensitizer in combination with topoisomerase inhibitors; as a chemosensitizer in combination with 5-fluorouracil; as a chemosensitizer in combination with curcumin; as

a chemosensitizer in combination with NF-κB inhibitors; as a chemosensitizer in combination with rosmarinic acid; as a chemosensitizer in combination with mitoguazone; as a chemosensitizer in combination with tetrandrine; as a chemosensitizer in combination with a tyrosine kinase inhibitor; as a chemosensitizer in combination with an EGFR inhibitor; or as a chemosensitizer in combination with an inhibitor of poly (ADP-ribose) polymerase (PARP).

[0101] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by exploiting the substituted hexitol derivative such as dianhydrogalactitol as a chemopotentiator where minimal therapeutic activity is observed alone but in combination with other therapeutics a more than additive or synergistic improvement in efficacy is observed. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: as a chemopotentiator in combination with topoisomerase inhibitors; as a chemopotentiator in combination with fraudulent nucleosides; as a chemopotentiator in combination with thymidylate synthetase inhibitors; as a chemopotentiator in combination with signal transduction inhibitors; as a chemopotentiator in combination with cisplatin, oxaliplatin, or other platinum analogs; as a chemopotentiator in combination with use with alkylating agents such as BCNU, BCNU wafers, Gliadel, or bendamustine (Treanda); as a chemopotentiator in combination with anti-tubulin agents; as a chemopotentiator in combination with antimetabolites; as a chemopotentiator in combination with berberine; as a chemopotentiator in combination with apigenin; as a chemopotentiator in combination with amonafide; as a chemopotentiator in combination with colchicine or analogs; as a chemopotentiator in combination with genistein; as a chemopotentiator in combination with etoposide; as a chemopotentiator in combination with cytarabine; as a chemopotentiator in combination with camptothecins; as a chemopotentiator in combination with vinca alkaloids; as a chemopotentiator in combination with topoisomerase inhibitors; as a chemopotentiator in combination with 5-fluorouracil; as a chemopotentiator in combination with curcumin; as a chemopotentiator in combination with NF-κB inhibitors; as a chemopotentiator in combination with rosmarinic acid; as a

chemopotentiator in combination with mitoguazone; as a chemopotentiator in combination with tetrandrine; as a chemopotentiator in combination with a tyrosine kinase inhibitor; as a chemopotentiator in combination with an EGFR inhibitor; or as a chemopotentiator in combination with an inhibitor of poly (ADP-ribose) polymerase (PARP).

[0102] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by drugs, treatments and diagnostics to allow for the maximum benefit to patients treated with a compound. General examples include: pain management, nutritional support, anti-emetics, anti-nausea therapies, anti-anemia therapy, anti-inflammatories. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: use with therapies associated with pain management; nutritional support; anti-emetics; anti-nausea therapies; anti-anemia therapy; anti-inflammatories: antipyretics; immune stimulants.

[0103] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by the use of complementary therapeutics or methods to enhance effectiveness or reduce side effects. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: hypnosis; acupuncture; meditation; herbal medications created either synthetically or through extraction including NF-κB inhibitors (such as parthenolide, curcumin, rosmarinic acid); natural anti-inflammatories (including rhein, parthenolide); immunostimulants (such as those found in Echinacea); antimicrobials (such as berberine); flavonoids, isoflavones, and flavones (such as apigenenin, genistein, genistin, 6″-O-malonylgenistin, 6″-O-acetylgenistin, daidzein, daidzin, 6″-O-malonyldaidzin, 6″-O-acetylgenistin, glycitein, glycitin, 6″-O-malonylglycitin, and 6-O-acetylglycitin); applied kinesiology.

[0104] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations in the pharmaceutical bulk substance.

General examples include: salt formation, homogeneous crystalline structure, pure isomers. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: salt formation; homogeneous crystalline structure; pure isomers; increased purity; lower residual solvents; or lower heavy metals.

[0105] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol or ovarian cancer for treatment of NSCLC made by alterations in the diluents used to solubilize and deliver/present the compound for administration. General examples include: Cremophor-EL, cyclodextrins for poorly water soluble compounds. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: use of emulsions; dimethyl sulfoxide (DMSO); N-methylformamide (NMF); dimethylformamide (DMF); dimethylacetamide (DMA); ethanol; benzyl alcohol; dextrose containing water for injection; Cremophor; cyclodextrins; PEG.

[0106] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC made by alterations in the solvents used or required to solubilize a compound for administration or for further dilution. General examples include: ethanol, dimethylacetamide (DMA). Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use of emulsions; DMSO; NMF; DMF; DMA; ethanol; benzyl alcohol; dextrose containing water for injection; Cremophor; cyclodextrin; or PEG.

[0107] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations in the materials/excipients, buffering agents, or preservatives required to stabilize and present a chemical compound for proper administration. General examples include: mannitol, albumin, EDTA, sodium bisulfite, benzyl alcohol. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use

of mannitol; albumin; EDTA; sodium bisulfite; benzyl alcohol; carbonate buffers; phosphate buffers.

[0108] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations in the potential dosage forms of the compound dependent on the route of administration, duration of effect, plasma levels required, exposure to side-effect normal tissues and metabolizing enzymes. General examples include: tablets, capsules, topical gels, creams, patches, suppositories. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use of tablets; capsules; topical gels; topical creams; patches; suppositories; lyophilized dosage fills.

[0109] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations in the dosage forms, container/closure systems, accuracy of mixing and dosage preparation and presentation. General examples include: amber vials to protect from light, stoppers with specialized coatings. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use of amber vials to protect from light; stoppers with specialized coatings to improve shelf-life stability.

[0110] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by the use of delivery systems to improve the potential attributes of a pharmaceutical product such as convenience, duration of effect, reduction of toxicities. General examples include: nanocrystals, bioerodible polymers, liposomes, slow release injectable gels, microspheres. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use of nanocrystals; bioerodible polymers; liposomes; slow release injectable gels; microspheres.

[0111] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment

of NSCLC or ovarian cancer made by alterations to the parent molecule with covalent, ionic, or hydrogen bonded moieties to alter the efficacy, toxicity, pharmacokinetics, metabolism, or route of administration. General examples include: polymer systems such as polyethylene glycols, polylactides, polyglycolides, amino acids, peptides, or multivalent linkers. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol or ovarian cancer for treatment of NSCLC include: the use of polymer systems such as polyethylene glycols; polylactides; polyglycolides; amino acids; peptides; multivalent linkers.

[0112] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by alterations to the molecule such that improved pharmaceutical performance is gained with a variant of the active molecule in that after introduction into the body a portion of the molecule is cleaved to reveal the preferred active molecule. General examples include: enzyme sensitive esters, dimers, Schiff bases. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use of enzyme sensitive esters; dimers; Schiff bases; pyridoxal complexes; caffeine complexes.

[0113] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by the use of additional compounds, biological agents that, when administered in the proper fashion, a unique and beneficial effect can be realized. General examples include: inhibitors of multi-drug resistance, specific drug resistance inhibitors, specific inhibitors of selective enzymes, signal transduction inhibitors, repair inhibition. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use of inhibitors of multi-drug resistance; specific drug resistance inhibitors; specific inhibitors of selective enzymes; signal transduction inhibitors; repair inhibition; topoisomerase inhibitors with non-overlapping side effects.

[0114] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment

of NSCLC or ovarian cancer made by the use of the substituted hexitol derivative such as dianhydrogalactitol in combination as sensitizers/potentiators with biological response modifiers. General examples include: use in combination as sensitizers/potentiators with biological response modifiers, cytokines, lymphokines, therapeutic antibodies, antisense therapies, gene therapies. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: use in combination as sensitizers/potentiators with biological response modifiers; cytokines; lymphokines; therapeutic antibodies such as Avastin, Herceptin, Rituxan, and Erbitux; antisense therapies; gene therapies; ribozymes; RNA interference; or vaccines.

[0115] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by exploiting the selective use of the substituted hexitol derivative such as dianhydrogalactitol to overcome developing or complete resistance to the efficient use of biotherapeutics. General examples include: tumors resistant to the effects of biological response modifiers, cytokines, lymphokines, therapeutic antibodies, antisense therapies, gene therapies. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use against tumors resistant to the effects of biological response modifiers; cytokines; lymphokines; therapeutic antibodies; antisense therapies; therapies such as Avastin, Rituxan, Herceptin, Erbitux; gene therapies; ribozymes; RNA interference; and vaccines.

[0116] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by exploiting their use in combination with ionizing radiation, phototherapies, heat therapies, or radio-frequency generated therapies. General examples include: hypoxic cell sensitizers, radiation sensitizers/protectors, photosensitizers, radiation repair inhibitors. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: use in combination with ionizing radiation; use in combination with hypoxic cell sensitizers; use in combination with radiation sensitizers/protectors;

use in combination with photosensitizers; use in combination with radiation repair inhibitors; use in combination with thiol depletion; use in combination with vaso-targeted agents; use in combination with use with radioactive seeds; use in combination with radionuclides; use in combination with radiolabeled antibodies; use in combination with brachytherapy. This is useful because radiation therapy is frequently employed in the treatment of NSCLC or ovarian cancer, especially for advanced disease, and improvements in the efficacy of such radiation therapy or the ability to exert a synergistic effect by combining radiation therapy with the administration of a substituted hexitol derivative such as dianhydrogalactitol is significant.

[0117] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by optimizing its utility by determining the various mechanisms of action, biological targets of a compound for greater understanding and precision to better exploit the utility of the molecule. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: the use with inhibitors of poly-ADP ribose polymerase; agents that effect vasculature or vasodilation; oncogenic targeted agents; signal transduction inhibitors; EGFR inhibition; Protein Kinase C inhibition; Phospholipase C downregulation; Jun downregulation; histone genes; VEGF; ornithine decarboxylase; ubiquitin C; jun D; v-jun; GPCRs; protein kinase A; telomerase, prostate specific genes; protein kinases other than protein kinase A; histone deacetylase; and tyrosine kinase inhibitors.

[0118] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by more precise identification and exposure of the compound to those select cell populations where the compound's effect can be maximally exploited, particularly NSCLC tumor cells or ovarian tumor cells. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include: use against radiation sensitive cells; use against radiation resistant cells; or use against energy depleted cells.

[0119] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer made by use of an agent that counteracts myelosuppression. Specific inventive examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer include use of dithiocarbamates to counteract myelosuppression.

[0120] Yet another aspect of the invention is an improvement in the therapeutic employment of a substituted hexitol derivative such as dianhydrogalactitol for treatment of brain metastases of NSCLC or ovarian cancer made by use of an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier. Specific examples for a substituted hexitol derivative such as dianhydrogalactitol for treatment of brain metastases of NSCLC or ovarian cancer include chimeric peptides; compositions comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative; neutral liposomes that are pegylated and that incorporate the substituted hexitol derivative and wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent; a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and a fusion protein linked to the hexitol through an avidin-biotin linkage.

[0121] Accordingly, one aspect of the present invention is a method to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer comprising the steps of:

(1) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the administration of the substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer; and

(2) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the substituted hexitol derivative such as dianhydrogalactitol for treatment of NSCLC or ovarian cancer.

[0122] In one alternative, the method improves the efficacy and/or reduces the side effects of the administration of the substituted hexitol derivative for treatment of

NSCLC. In another alternative, the method improves the efficacy and/or reduces the side effects of the administration of the substituted hexitol derivative for treatment of ovarian cancer.

[0123] Typically, the factor or parameter is selected from the group consisting of:

(1) dose modification;
(2) route of administration;
(3) schedule of administration;
(4) indications for use;
(5) selection of disease stage;
(6) other indications;
(7) patient selection;
(8) patient/disease phenotype;
(9) patient/disease genotype;
(10) pre/post-treatment preparation
(11) toxicity management;
(12) pharmacokinetic/pharmacodynamic monitoring;
(13) drug combinations;
(14) chemosensitization;
(15) chemopotentiation;
(16) post-treatment patient management;
(17) alternative medicine/therapeutic support;
(18) bulk drug product improvements;
(19) diluent systems;
(20) solvent systems;
(21) excipients;
(22) dosage forms;
(23) dosage kits and packaging;
(24) drug delivery systems;
(25) drug conjugate forms;
(26) compound analogs;
(27) prodrugs;

(28) multiple drug systems;

(29) biotherapeutic enhancement;

(30) biotherapeutic resistance modulation;

(31) radiation therapy enhancement;

(32) novel mechanisms of action;

(33) selective target cell population therapeutics;

(34) use with ionizing radiation;

(35) use of an agent that counteracts myelosuppression; and

(36) use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier to treat brain metastases of NSCLC or ovarian cancer.

[0124] As detailed above, in general, the substituted hexitol derivative usable in methods and compositions according to the present invention include galactitols, substituted galacitols, dulcitols, and substituted dulcitols, including dianhydrogalactitol, diacetyldianhydrogalactitol, dibromodulcitol, and derivatives and analogs thereof. Typically, the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol. Preferably, the substituted hexitol derivative is dianhydrogalactitol.

[0125] When the improvement made is by dose modification, the dose modification can be, but is not limited to, at least one dose modification selected from the group consisting of:

(a) continuous i.v. infusion for hours to days;

(b) biweekly administration;

(c) doses greater than 5 mg/m^2/day;

(d) progressive escalation of dosing from 1 mg/m^2/day based on patient tolerance;

(e) use of caffeine to modulate metabolism;

(f) use of isoniazid to modulate metabolism;

(g) selected and intermittent boosting of dosage administration;

(h) administration of single and multiple doses escalating from 5 mg/m^2/day via bolus;

(i) oral dosages of below 30 mg/m^2;

(j) oral dosages of above 130 mg/m^2;

(k) oral dosages up to 40 mg/m^2 for 3 days and then a nadir/recovery period of 18-21 days;

(l) dosing at a lower level for an extended period (e.g., 21 days);

(m) dosing at a higher level;

(n) dosing with a nadir/recovery period longer than 21 days;

(o) the use of a substituted hexitol derivative such as dianhydrogalactitol as a single cytotoxic agent, typically at 30 mg/m^2/day $\times$ 5 days, repeated monthly;

(p) dosing at 3 mg/kg;

(q) the use of a substituted hexitol derivative such as dianhydrogalactitol in combination therapy, typically at 30 mg/m^2/day $\times$ 5 days; and

(r) dosing at 40 mg/day $\times$ 5 days in adult patients, repeated every two weeks.

[0126] When the improvement is made by route of administration, the route of administration can be, but is not limited to, at least one route of administration selected from the group consisting of:

(a) topical administration;

(b) oral administration;

(c) slow release oral delivery;

(d) intrathecal administration;

(e) intraarterial administration;

(f) continuous infusion;

(g) intermittent infusion;

(h) intravenous administration, such as intravenous administration for 30 minutes;

(i) administration through a longer infusion; and

(j) administration through IV push.

[0127] When the improvement is made by schedule of administration, the schedule of administration can be, but is not limited to, at least one schedule of administration selected from the group consisting of:

(a) daily administration;

(b) weekly administration;

(c) weekly administration for three weeks;

(d) biweekly administration;

(e) biweekly administration for three weeks with a 1-2 week rest period;

(f) intermittent boost dose administration; and

(g) daily administration for one week for multiple weeks.

[0128] When the improvement is made by selection of disease stage, the selection of disease stage can be, but is not limited to, at least one selection of disease stage selected from the group consisting of:

(a) use in an appropriate disease stage for NSCLC or ovarian cancer;

(b) use with an angiogenesis inhibitor to prevent or limit metastatic spread;

(c) use for newly diagnosed disease;

(d) use for recurrent disease; and

(e) use for resistant or refractory disease.

[0129] When the improvement is made by patient selection, the patient selection can be, but is not limited to, a patient selection carried out by a criterion selected from the group consisting of:

(a) selecting patients with a disease condition characterized by a high level of a metabolic enzyme selected from the group consisting of histone deacetylase and ornithine decarboxylase;

(b) selecting patients with a low or high susceptibility to a condition selected from the group consisting of thrombocytopenia and neutropenia;

(c) selecting patients intolerant of GI toxicities;

(d) selecting patients characterized by over- or under-expression of a gene selected from the group consisting of c-Jun, a GPCR, a signal transduction protein, VEGF, a prostate-specific gene, and a protein kinase.

(e) selecting patients characterized by carrying extra copies of the EGFR gene for NSCLC;

(f) selecting patients characterized by methylation or lack of methylation of the promoter of the MGMT gene;

(g) selecting patients characterized by an unmethylated promoter region of MGMT (O^6-methylguanine methyltransferase);

(h) selecting patients characterized by a methylated promoter region of MGMT;

(i) selecting patients characterized by a high expression of MGMT;

(j) selecting patients characterized by a low expression of MGMT;

(k) selecting patients characterized by a mutation in EGFR, including, but not limited to EGFR Variant III;

(l) selecting patients being administered a platinum-based drug as combination therapy;

(m) selecting patients who do not have EGFR mutations and thus are less likely to respond to tyrosine kinase inhibitors (TKI);

(n) selecting patients who have become resistant to TKI treatment;

(o) selecting patients who have the *BIM* co-deletion mutation and thus are less likely to respond to TKI treatment;

(p) selecting patients who have become resistant to platinum-based drug treatment; and

(q) selecting patients with brain metastases.

[0130] The cellular proto-oncogene c-Jun encodes a protein that, in combination with c-Fos, forms the AP-1 early response transcription factor. This proto-oncogene plays a key role in transcription and interacts with a large number of proteins affecting

transcription and gene expression. It is also involved in proliferation and apoptosis of cells that form part of a number of tissues, including cells of the endometrium and glandular epithelial cells. G-protein coupled receptors (GPCRs) are important signal transducing receptors. The superfamily of G protein coupled receptors includes a large number of receptors. These receptors are integral membrane proteins characterized by amino acid sequences that contain seven hydrophobic domains, predicted to represent the transmembrane spanning regions of the proteins. They are found in a wide range of organisms and are involved in the transmission of signals to the interior of cells as a result of their interaction with heterotrimeric G proteins. They respond to a diverse range of agents including lipid analogues, amino acid derivatives, small molecules such as epinephrine and dopamine, and various sensory stimuli. The properties of many known GPCR are summarized in S. Watson & S. Arkinstall, "The G-Protein Linked Receptor Facts Book" (Academic Press, London, 1994), incorporated herein by this reference. GPCR receptors include, but are not limited to, acetylcholine receptors, β-adrenergic receptors, β_3-adrenergic receptors, serotonin (5-hydroxytryptamine) receptors, dopamine receptors, adenosine receptors, angiotensin Type II receptors, bradykinin receptors, calcitonin receptors, calcitonin gene-related receptors, cannabinoid receptors, cholecystokinin receptors, chemokine receptors, cytokine receptors, gastrin receptors, endothelin receptors, γ-aminobutyric acid (GABA) receptors, galanin receptors, glucagon receptors, glutamate receptors, luteinizing hormone receptors, choriogonadotrophin receptors, follicle-stimulating hormone receptors, thyroid-stimulating hormone receptors, gonadotrophin-releasing hormone receptors, leukotriene receptors, Neuropeptide Y receptors, opioid receptors, parathyroid hormone receptors, platelet activating factor receptors, prostanoid (prostaglandin) receptors, somatostatin receptors, thyrotropin-releasing hormone receptors, vasopressin and oxytocin receptors.

[0131] EGFR mutations can be associated with sensitivity to therapeutic agents such as gefitinib, as described in J.G. Paez et al., "EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib," Science 304: 1497-1500 (2004), incorporated herein by this reference. One specific mutation in EGFR that is associated with resistance to tyrosine kinase inhibitors is known as EGFR Variant III, which is

described in C.A. Learn et al., "Resistance to Tyrosine Kinase Inhibition by Mutant Epidermal Growth Factor Variant III Contributes to the Neoplastic Phenotype of Glioblastoma Multiforme," Clin. Cancer Res. 10: 3216-3224 (2004), incorporated herein by this reference. EGFR Variant III is characterized by a consistent and tumor-specific in-frame deletion of 801 bp from the extracellular domain that splits a codon and produces a novel glycine at the fusion junction. This mutation encodes a protein with a constituently active thymidine kinase that enhances the tumorigenicity of the cells carrying this mutation. This mutated protein sequence is absent from normal tissues.

[0132] Recent work has established that resistance to TKI (tyrosine kinase inhibitor) chemotherapy is at least partially due to genetic polymorphisms that affect the apoptotic response to TKI.

[0133] Specifically, these polymorphisms include, but are not necessarily limited to, polymorphisms in the gene *BCL2L11* (also known as *BIM*), which encodes a BH3-only protein that is a BCL-2 family member. The BH3-only proteins activate cell death by either opposing the prosurvival members of the BCL2 family (BCL2, BCL2-like 1 (BCL-XL, also known as BCL2L1), myeloid cell leukemia sequence 1 (MCL1) and BCL2-related protein A1 (BCL2A1)) or by binding to the pro-apoptotic BCL2 family members (BCL2-associated X protein (BAX) and BCL2-antagonist/killer 1 (BAK1)) and directly activating their pro-apoptotic functions; the activation of pro-apoptotic functions would result in cell death (R.J. Youle & A. Strasser, "The BCL-2 Protein Family: Opposing Activities that Mediate Cell Death," Nat. Rev. Mol. Cell. Biol. 9: 47-59 (2008), incorporated herein by this reference.

[0134] It also has been previously shown that several kinase-driven cancers, such as CML and EGFR NSCLC, can maintain a survival advantage by suppressing *BIM* transcription and also by targeting BIM protein for proteasomal degradation through mitogen-activated protein kinase 1 (MAPK-1)-dependent phosphorylation. In all of these malignancies, BIM upregulation is required for TKIs to induce apoptosis of cancer cells, and suppression of BIM expression is sufficient to confer *in vitro* resistance to TKIs (J. Kuroda et al., "Bim and Bad Mediate Imatinib-Induced Killing of Bcr/Abl$^+$ Leukemic Cells, and Resistance Due to Their Loss is Overcome by a BH3 Mimetic," Proc. Natl. Acad. Sci. USA 103: 14907-14912 (2006); K.J. Aichberger et al., "Low-Level

Expression of Proapoptotic Bcl-2-Interacting Mediator in Leukemic Cells in Patients with Chronic Myeloid Leukemia: Role of BCR/ABL, Characterization of Underlying Signaling Pathways, and Reexpression by Novel Pharmacologic Compounds," Cancer Res. 65: 9436-9444 (2005); R. Kuribara et al., "Roles of Bim in Apoptosis of Normal and Bcl-Abr-Expressing Hematopoietic Progenitors," Mol. Cell. Biol. 24: 6172-6183 (2004); M.S. Cragg et al., "Gefitinib-Induced Killing of NSCLC Cell Lines Expressing Mutant EGFR Requires BIM and Can Be Enhanced by BH3 Mimetics," PLoS Med. 4: 1681-1689 (2007); Y. Gong et al., "Induction of BIM Is Essential for Apoptosis Triggered by EGFR Kinase Inhibitors in Mutant EGFR-Dependent Lung Adenocarcinomas," PLoS Med. 4: e294 (2007); D.B. Costa et al., "BIM Mediates EGFR Tyrosine Kinase Inhibitor-Induced Apoptosis in Lung Cancers with Oncogenic EGFR Mutations," PLoS Med. 4: 1669-1679 (2007), all of which are incorporated herein by this reference).

[0135] One recent finding has been the discovery of a deletion polymorphism in the *BIM* gene that results in the generation of alternatively spliced isoforms of BIM that lack the crucial BH3 domain that is involved in the promotion of apoptosis. This polymorphism has a profound effect on the TKI sensitivity of CML and EGFR NSCLC cells, such that one copy of the deleted allele is sufficient to render cells intrinsically TKI resistant. This polymorphism therefore functions in a dominant manner to render such cells resistant to TKI chemotherapy. This finding also includes the result that individuals with the polymorphism have markedly inferior responses to TKI than do individuals without the polymorphism. In particular, the presence of the polymorphism was correlated with a lesser degree of response to imatinib, a TKI, in CML, as well as a shorter progression-free survival (PFS) with EGFR TKI therapy in EGFR NSCLC (K.P. Ng et al., "A Common *BIM* Deletion Polymorphism Mediates Intrinsic Resistance and Inferior Responses to Tyrosine Kinase Inhibitors in Cancer," Nature Med. doi 10.138/nm.2713 (March 18, 2012), incorporated herein by this reference).

[0136] When the method is intended to treat NSCLC, other biomarkers are known that are specific for the prognosis or staging of NSCLC and that can be used. Predictive biomarkers for NSCLC are disclosed in F.R. Hirsch et al., "Molecular Predictors of Outcome With Gefitinib in a Phase III Placebo-Controlled Study in Advanced Non-Small-Cell Lung Cancer," J. Clin. Oncol. 24: 5034-5042 (2006),

incorporated herein by this reference. These biomarkers include: (i) EGFR gene copy number; (ii) the presence of EGFR mutations, including Exon 18 G719A; Exon 19 deletion; Exon 19 A743S; and Exon 21 L858R/L861Q; (iii) EGFR protein expression; (iv) p-Akt protein expression; (v) the presence of *KRAS* mutations; and (vi) the presence of *BRAF* mutations. Other biomarkers are described in M. Cobo et al., "Customizing Cisplatin Based on Quantitative Excision Repair Cross-Complementing 1 mRNA Expression: A Phase III Trial in Non-Small-Cell Lung Cancer," J. Clin. Oncol. 25: 2747-2754 (2006), incorporated herein by this reference, including mRNA levels for ERCC1.

[0137] Still other biomarkers for NSCLC are known in the art. United States Patent No. 8,969,001 to Buckingham discloses DNA methylation as a biomarker for NSCLC. United States Patent No. 8,940,302 to Amler et al. discloses the existence of low HER3 as a biomarker for NSCLC. United States Patent No. 8,911,940 to Weiss et al. discloses miRNA expression as a biomarker for NSCLC. United States Patent No. 8,828,657 to Rafnar et al. discloses genetic variants as biomarkers for NSCLC, including the alleles rs1051730 allele T, rs16969968 allele A, ss107794645 allele C, and rs8034191 allele C. United States Patent No. 8,768,629 to Von Hoff et al. discloses TOP1, TYMS, MGMT, PTEN, ERBB2, and SPARC as biomarkers for NSCLC. United States Patent No. 8,741,587 to Roessler et al. discloses a protein known as arginine-rich metastasized in early tumors protein (ARMET) as a biomarker for NSCLC. United States Patent No. 8,728,823 to Lam et al. discloses CTAP-III related biomarkers as biomarkers for NSCLC. United States Patent No. 8,700,335 to Von Hoff et al. discloses ERBB2, ESR1, PGR, KIT, EGFR, PTGS2 and AR as biomarkers for NSCLC. United States Patent No. 8,632,592 to Schoeberl discloses pErbB3 as a biomarker for NSCLC; pErbB3 is determined by indirect measurement that includes: measuring total protein in the sample and levels of (i) at least one receptor selected from ErbB1, ErbB2, and ErbB3 and (ii) at least one of heregulin and betacellulin. United States Patent No. 8,476,420 to Showe et al. discloses gene expression profiles as biomarkers for NSCLC. United States Patent No. 8,377,888 to Costa et al. discloses the methylation state of nucleic acid encoding 14-3-3 sigma as a biomarker for NSCLC. United States Patent No. 8,211,643 to Tsao et al. discloses a multigene signature as a biomarker for NSCLC. United States Patent No. 8,133,692 to Jove et al. discloses phosphorylated Stat and

expression of survivin as biomarkers for NSCLC. United States Patent No. 7,655,414 to Brennscheidt et al. discloses overexpression of a phosphorylated AKT protein and/or a phosphorylated MAPK protein as biomarkers for NSCLC. These biomarkers, and others known in the art, can be used for patient selection.

[0138] When the method is intended to treat ovarian cancer, other biomarkers are known that are specific for the prognosis or staging of ovarian cancer and that can be used. Biomarkers for ovarian cancer are disclosed in B. Zhang et al., "An Overview of Biomarkers for the Ovarian Cancer Diagnosis," Eur. J. Obstet. Gynecol. Reprod. Biol. 2: 119-123 (2011), incorporated herein by this reference. These biomarkers include mutations in *BRCA1* or *BRCA2*; hypermethylation of *BRCA1*, *RASSF1A*, *APC*, *p14ARF*, *p16INK4a*, or *DAPkinase*; gene expression profiles specific for ovarian cancer; profiles derived from serial analysis of gene expression (SAGE) for *CLDN3*, *HE4*, *FOLR1*, *COL18A1*, *CCND1*, or *FLJ12988*; cleavage fragment of inter-α-trypsin inhibitor heavy chain H4; transferrin; afamin; apoliprotein A-IV; and miRNA expression profiles. Another biomarker that has been used frequently for ovarian cancer is the protein CA125. CA125 is a heavily glycosylated protein of 1890 amino acids that is typically assayed in serum. Still another biomarker that has been used for ovarian cancer is the protein DF3; this protein is also typically assayed in serum.

[0139] Still other biomarkers for ovarian cancer are known in the art. United States Patent No. 8,741,641 to Inazawa et al. discloses alterations of a gene existing in a chromosomal region 2q14.2, 3p24.1, 3q26.2, 3q29, 4q34.2, 6q23, 9p21 3, 11q13.3, 13q22.1, 13q33.1, 13q33.3, 15q12, 15q15.1, 17p12, 17p13.1, 17p13.3, 18q21.1, 18q21.2, 18q21.31, 18q21.32, 18q21.33, 18q23, 20q13.13, 20q13.2, 20q13.31, 20q13.33, Xp11.23, Xp13.1, Xp13.3, Xp26.2, Xp26.3, or Xq28 as biomarkers for ovarian cancer. United States Patent No. 8,682,591 to Chan et al. discloses biomarkers for ovarian cancer including modified ApoA1 and one or more modified transthyretin selected from the group consisting of cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin. United States Patent No. 8,664,358 to Mansfield et al. discloses a number of biomarkers for ovarian cancer, including CA-125, CRP, EGF-R, CA-19-9, Apo-AI, Apo-CIII, IL-6, IL-18, MIP-1a, tenascin C and myoglobin, and fragments thereof. United States Patent No.

8,652,777 to Kamalakaran et al. discloses the methylation status of CpG dinucleotides as a biomarker for ovarian cancer. United States Patent No. 8,642,347 to Ye et al. discloses peptides derived from the degradation of CA125 present in the urine as biomarkers for ovarian cancer. United States Patent No. 8,476,026 to Alex et al. discloses that antibodies for a number of antigens are biomarkers for ovarian cancer; the antigens include casein kinase 1. United States Patent No. 8,465,929 to Fung et al. discloses a number of biomarkers for ovarian cancer, including calcyclin, calgranulin C, hepcidin, ApoC1, ApoAII, ApoCII, calgranulin A, and transthyretin. United States Patent No. 8,404,829 to Gray et al. discloses elevated expression of *PVT1* as a biomarker for ovarian cancer. United States Patent No. 8,323,906 to Veiby et al. discloses the use of LIV-1 as a biomarker for ovarian cancer. United States Patent No. 8,192,935 to Al-Murrani discloses the expression level of *MetAP2* as a biomarker for cisplatin resistance in ovarian cancer. United States Patent No. 8,030,060 to Guo discloses gene signatures as biomarkers for prediction of recurrence and metastasis in ovarian cancer, including a 15-gene signature, a 23-gene signature, and a 28-gene signature. United States Patent No. 7,910,314 to Frackelton, Jr. et al. discloses p66-Shc and phosphorylated Shc as biomarkers for ovarian cancer. United States Patent No. 7,700,280 to Al-Murrani discloses the expression level of *S100A10* and *S100A11* as biomarkers for cisplatin resistance in ovarian cancer. United States Patent No. 7,507,800 to van Ommen et al. discloses germline deletions of *BRCA1* as biomarkers for ovarian cancer. United States Patent No. 7,507,536 to Van Kriekinge et al. discloses epigenetic silencing of a number of genes as biomarkers for ovarian cancer, including the genes encoding plasmolipin, TNFRSF10B tumor necrosis factor receptor superfamily (member 10b), RUNX3 runt-related transcription factor 3, ACTN1 actinin (alpha 1), and FANCG Fanconi anemia (complementation group G). United States Patent Application Publication No. 2015/0080249 by Lancaster et al. discloses the use of an elevated expression level of a number of genes involved in the O-glycan pathway as biomarkers for ovarian cancer; these genes include *B3GALT1*, *B3GALT2*, *B3GALT4*, *B3GALT5*, *B3GNT6*, *B4GALT1*, *B4GALT2*, *B4GALT3*, *C1GALT1*, *GALNT1*, *GALNT10*, *GALNT11*, *GALNT12*, *GALNT13*, *GALNT14*, *GALNT2*, *GALNT3*, *GALNT4*, *GALNT5*, *GALNT6*, *GALNT7*, *GALNT8*, *GALNT9*, *GALNTL1*, *GALNTL2*, *GALNTL4*, *GALNTL5*,

GCNT1, *GCNT2*, *GCNT3*, *ST3GAL1*, *ST3GAL2*, *ST6GALN*, and *WBSCR17*. United States Patent Application Publication No. 2015/0031561 by Bertenshaw et al. discloses a number of biomarkers for ovarian cancer, including CA125, HE4, IL-2Rα, α-1-antitrypsin, C-reactive protein, YKL-40, cellular fibronectin, prostasin, TIMP-1, IL-8, IL-6, VEGF-B, MMP-7, calprotectin, IGFBP-2, LOX-1, neuropilin-1, TNFR2, MPIF-1, and CA-72-4. United States Patent Application Publication No. 2014/0364341 by Bertenshaw et al. discloses a number of biomarkers for ovarian cancer including CA 15-3 (MUC-1), Her2/Neu (erbB-2), kallikrein-5, Macrophage Inhibitory Factor (MIF), osteopontin, TAG-72, IGF-II, HE4, IL6-R, IL18-R, IL-18BP, VCAM-1, IP-10 (interferon-gamma inducible 10 kD protein), SMRP, TgII (tissue transglutaminase), exotaxin-1, Cyfra 21-1(cytokeratin 19 fragment), IGF2BP3, TIMP-1, alpha-1 antitrypsin, MMP7, IL-8, IL-6, sortillin, CD40, Alpha 1-Antichymotrypsin, VEGF, and haptoglobin. United States Patent Application Publication No. 2014/0017703 by Lancaster et al. discloses that the phosphorylation level of a BCL2 antagonist of cell death pathway protein can be used as a biomarker for predicting clinical outcome of platinum-based cancer treatment, taxane cancer treatment, or cyclophosphamide treatment, wherein the BCL2 antagonist of cell death pathway protein is BAD, Bax, BcL-XL, PP2C/PPM1A, AKT, EGFR, IRS-1, Shc, H-Ras, CDK1, G-protein alpha-s, G-protein beta/gamma, PI3K cat class 1A, c-Raf-1, p90Rsk, MEK2 (MAP2K2), PKA-cat, or PKA-reg.

[0140] When the improvement is made by analysis of patient or disease phenotype, the analysis of patient or disease phenotype can be, but is not limited to, a method of analysis of patient or disease phenotype carried out by a method selected from the group consisting of:

(a) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular phenotype;

(b) use of a method for measurement of a marker selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a protein that is a gene product of jun, and a protein kinase;

(c) surrogate compound dosing; and

(d) low dose pre-testing for enzymatic status.

[0141] When the improvement is made by analysis of patient or disease genotype, the analysis of patient or disease genotype can be, but is not limited to, a method of analysis of patient or disease genotype carried out by a method selected from the group consisting of:

(a) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular genotype;

(b) use of a gene chip;

(c) use of gene expression analysis;

(d) use of single nucleotide polymorphism (SNP) analysis;

(e) measurement of the level of a metabolite or a metabolic enzyme;

(f) determination of copy number of the EGFR gene;

(g) determination of status of methylation of promoter of MGMT gene;

(h) determination of the existence of an unmethylated promoter region of the MGMT gene;

(i) determination of the existence of a methylated promoter region of the MGMT gene;

(j) determination of the existence of high expression of MGMT;

(k) determination of the existence of low expression of MGMT; and

(l) for ovarian cancer, determination of the genotype status of p53.

[0142] The use of gene chips is described in A.J. Lee & S. Ramaswamy, "DNA Microarrays in Biological Discovery and Patient Care" in Essentials of Genomic and Personalized Medicine (G.S. Ginsburg & H.F. Willard, eds., Academic Press, Amsterdam, 2010), ch. 7, pp. 73-88, incorporated herein by this reference.

[0143] When the method is the use of single nucleotide polymorphism (SNP) analysis, the SNP analysis can be carried out on a gene selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a prostate specific gene, c-Jun, and a protein kinase. The use of SNP analysis is described in S. Levy and

Y.-H. Rogers, "DNA Sequencing for the Detection of Human Genome Variation" in Essentials of Genomic and Personalized Medicine (G.S. Ginsburg & H.F. Willard, eds., Academic Press, Amsterdam, 2010), ch. 3, pp. 27-37, incorporated herein by this reference.

[0144] Still other genomic techniques such as copy number variation analysis and analysis of DNA methylation can be employed. Copy number variation analysis is described in C. Lee et al., "Copy Number Variation and Human Health" in Essentials of Genomic and Personalized Medicine (G.S. Ginsburg & H.F. Willard, eds., Academic Press, Amsterdam, 2010), ch. 5, pp. 46-59, incorporated herein by this reference. DNA methylation analysis is described in S. Cottrell et al., "DNA Methylation Analysis: Providing New Insight into Human Disease" in Essentials of Genomic and Personalized Medicine (G.S. Ginsburg & H.F. Willard, eds., Academic Press, Amsterdam, 2010), ch. 6, pp. 60-72, incorporated herein by this reference. This is particularly significant for NSCLC in that the prognosis for NSCLC can vary with the degree of methylation of the promoter of the MGMT gene because of the role of the MGMT gene in promoting drug resistance.

[0145] When the improvement is made by pre/post-treatment preparation, the pre/post-treatment preparation can be, but is not limited to, a method of pre/post treatment preparation selected from the group consisting of:

(a) the use of colchicine or an analog thereof;
(b) the use of a diuretic;
(c) the use of a uricosuric;
(d) the use of uricase;
(e) the non-oral use of nicotinamide;
(f) the use of a sustained-release form of nicotinamide;
(g) the use of an inhibitor of poly-ADP ribose polymerase;
(h) the use of caffeine;
(i) the use of leucovorin rescue;
(j) infection control; and
(k) the use of an anti-hypertensive agent.

[0146] Uricosurics include, but are not limited to, probenecid, benzbromarone, and sulfinpyrazone. A particularly preferred uricosuric is probenecid. Uricosurics, including probenecid, may also have diuretic activity. Other diuretics are well known in the art, and include, but are not limited to, hydrochlorothiazide, carbonic anhydrase inhibitors, furosemide, ethacrynic acid, amiloride, and spironolactone.

[0147] Poly-ADP ribose polymerase inhibitors are described in G.J. Southan & C. Szabó, "Poly(ADP-Ribose) Inhibitors," Curr. Med. Chem. 10: 321-240 (2003), incorporated herein by this reference, and include nicotinamide, 3-aminobenzamide, substituted 3,4-dihydroisoquinolin-1(2H)-ones and isoquinolin-1(2H)-ones, benzimidazoles, indoles, phthalazin-1(2H)-ones, quinazolinones, isoindolinones, phenanthridinones, and other compounds.

[0148] Leucovorin rescue comprises administration of folinic acid (leucovorin) to patients in which methotrexate has been administered. Leucovorin is a reduced form of folic acid that bypasses dihydrofolate reductase and restores hematopoietic function. Leucovorin can be administered either intravenously or orally.

[0149] In one alternative, wherein the pre/post treatment is the use of a uricosuric, the uricosuric is probenecid or an analog thereof.

[0150] When the improvement is made by toxicity management, the toxicity management can be, but is not limited to, a method of toxicity management selected from the group consisting of:

(a) the use of colchicine or an analog thereof;
(b) the use of a diuretic;
(c) the use of a uricosuric;
(d) the use of uricase;
(e) the non-oral use of nicotinamide;
(f) the use of a sustained-release form of nicotinamide;
(g) the use of an inhibitor of poly-ADP ribose polymerase;
(h) the use of caffeine;
(i) the use of leucovorin rescue;
(j) the use of sustained-release allopurinol;
(k) the non-oral use of allopurinol;

(l) the use of bone marrow transplants;

(m) the use of a blood cell stimulant;

(n) the use of blood or platelet infusions;

(o) the administration of an agent selected from the group consisting of filgrastim, G-CSF, and GM-CSF;

(p) the application of a pain management technique;

(q) the administration of an anti-inflammatory agent;

(r) the administration of fluids;

(s) the administration of a corticosteroid;

(t) the administration of an insulin control medication;

(u) the administration of an antipyretic;

(v) the administration of an anti-nausea treatment;

(w) the administration of an anti-diarrheal treatment;

(x) the administration of N-acetylcysteine; and

(y) the administration of an antihistamine.

[0151] Filgrastim is a granulocytic colony-stimulating factor (G-CSF) analog produced by recombinant DNA technology that is used to stimulate the proliferation and differentiation of granulocytes and is used to treat neutropenia; G-CSF can be used in a similar manner. GM-CSF is granulocyte macrophage colony-stimulating factor and stimulates stem cells to produce granulocytes (eosinophils, neutrophils, and basophils) and monocytes; its administration is useful to prevent or treat infection.

[0152] Anti-inflammatory agents are well known in the art and include corticosteroids and non-steroidal anti-inflammatory agents (NSAIDs). Corticosteroids with anti-inflammatory activity include, but are not limited to, hydrocortisone, cortisone, beclomethasone dipropionate, betamethasone, dexamethasone, prednisone, methylprednisolone, triamcinolone, fluocinolone acetonide, and fludrocortisone. Non-steroidal anti-inflammatory agents include, but are not limited to, acetylsalicylic acid (aspirin), sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, olsalazine, acetaminophen, indomethacin, sulindac, tolmetin, diclofenac, ketorolac, ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofin, oxaprozin, mefenamic acid, meclofenamic acid, piroxicam, meloxicam, nabumetone, rofecoxib,

celecoxib, etodolac, nimesulide, aceclofenac, alclofenac, alminoprofen, amfenac, ampiroxicam, apazone, araprofen, azapropazone, bendazac, benoxaprofen, benzydamine, bermoprofen, benzpiperylon, bromfenac, bucloxic acid, bumadizone, butibufen, carprofen, cimicoxib, cinmetacin, cinnoxicam, clidanac, clofezone, clonixin, clopirac, darbufelone, deracoxib, droxicam, eltenac, enfenamic acid, epirizole, esflurbiprofen, ethenzamide, etofenamate, etoricoxib, felbinac, fenbufen, fenclofenac, fenclozic acid, fenclozine, fendosal, fentiazac, feprazone, filenadol, flobufen, florifenine, flosulide, flubichin methanesulfonate, flufenamic acid, flufenisal, flunixin, flunoxaprofen, fluprofen, fluproquazone, furofenac, ibufenac, imrecoxib, indoprofen, isofezolac, isoxepac, isoxicam, licofelone, lobuprofen, lomoxicam, lonazolac, loxaprofen, lumiracoxib, mabuprofen, miroprofen, mofebutazone, mofezolac, morazone, nepafanac, niflumic acid, nitrofenac, nitroflurbiprofen, nitronaproxen, orpanoxin, oxaceprol, oxindanac, oxpinac, oxyphenbutazone, pamicogrel, parcetasal, parecoxib, parsalmide, pelubiprofen, pemedolac, phenylbutazone, pirazolac, pirprofen, pranoprofen, salicin, salicylamide, salicylsalicylic acid, satigrel, sudoxicam, suprofen, talmetacin, talniflumate, tazofelone, tebufelone, tenidap, tenoxicam, tepoxalin, tiaprofenic acid, tiaramide, tilmacoxib, tinoridine, tiopinac, tioxaprofen, tolfenamic acid, triflusal, tropesin, ursolic acid, valdecoxib, ximoprofen, zaltoprofen, zidometacin, and zomepirac, and the salts, solvates, analogues, congeners, bioisosteres, hydrolysis products, metabolites, precursors, and prodrugs thereof.

[0153] The clinical use of corticosteroids is described in B.P. Schimmer & K.L. Parker, "Adrenocorticotropic Hormone; Adrenocortical Steroids and Their Synthetic Analogs; Inhibitors of the Synthesis and Actions of Adrenocortical Hormones" in Goodman & Gilman's The Pharmacological Basis of Therapeutics (L.L. Brunton, ed., 11th ed., McGraw-Hill, New York, 2006), ch. 59, pp. 1587-1612, incorporated herein by this reference.

[0154] Anti-nausea treatments include, but are not limited to, ondansetron, metoclopramide, promethazine, cyclizine, hyoscine, dronabinol, dimenhydrinate, diphenhydramine, hydroxyzine, medizine, dolasetron, granisetron, palonosetron, ramosetron, domperidone, haloperidol, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, betamethasone, dexamethasone, lorazepam, and thiethylperazine.

[0155] Anti-diarrheal treatments include, but are not limited to, diphenoxylate, difenoxin, loperamide, codeine, racecadotril, octreoside, and berberine.

[0156] N-acetylcysteine is an antioxidant and mucolytic that also provides biologically accessible sulfur.

[0157] Poly-ADP ribose polymerase (PARP) inhibitors include, but are not limited to: (1) derivatives of tetracycline as described in United States Patent No. 8,338,477 to Duncan et al.; (2) 3,4-dihydro-5-methyl-1(2*H*)-isoquinoline, 3-aminobenzamide, 6-aminonicotinamide, and 8-hydroxy-2-methyl-4(3*H*)-quinazolinone, as described in United States Patent No. 8,324,282 by Gerson et al.; (3) 6-(5*H*)-phenanthridinone and 1,5-isoquinolinediol, as described in United States Patent No. 8,324,262 by Yuan et al.; (4) (R)-3-[2-(2-hydroxymethylpyrrolidin-1-yl)ethyl]-5-methyl-2H-isoquinolin-1-one, as described in United States Patent No. 8,309,573 to Fujio et al.; (5) 6-alkenyl-substituted 2-quinolinones, 6-phenylalkyl-substituted quinolinones, 6-alkenyl-substituted 2-quinoxalinones, 6-phenylalkyl-substituted 2-quinoxalinones, substituted 6-cyclohexylalkyl substituted 2-quinolinones, 6-cyclohexylalkyl substituted 2-quinoxalinones, substituted pyridones, quinazolinone derivatives, phthalazine derivatives, quinazolinedione derivatives, and substituted 2-alkyl quinazolinone derivatives, as described in United States Patent No. 8,299,256 to Vialard et al.; (6) 5-bromoisoquinoline, as described in United States Patent No. 8,299,088 to Mateucci et al.; (7) 5-bis-(2-chloroethyl)amino]-1-methyl-2-benzimidazolebutyric acid, 4-iodo-3-nitrobenzamide, 8-fluoro-5-(4-((methylamino)methyl)phenyl)-3,4-dihydro-2H-azepino[5,4,3-cd]indol-1(6H)-one phosphoric acid, and N-[3-(3,4-dihydro-4-oxo-1-phthalazinyl)phenyl]-4-morpholinebutanamide methanesulfonate, as described in United States Patent No. 8,227,807 to Gallagher et al.; (8) pyridazinone derivatives, as described in United States Patent No. 8,268,827 to Branca et al.; (9) 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluorobenzyl]-2H-phthalazin-1-one, as described in United States Patent No. 8,247,416 to Menear et al.; (10) tetraaza phenalen-3-one compounds, as described in United States Patent No. 8,236,802 to Xu et al.; (11) 2-substituted-1*H*-benzimidazole-4-carboxamides, as described in United States Patent No. 8,217,070 to Zhu et al.; (12) substituted 2-alkyl quinazolinones, as described in United States Patent No. 8,188,103 to Van der Aa et al.; (13) 1*H*-

benzimidazole-4-carboxamides, as described in United States Patent No. 8,183,250 to Penning et al.; (14) indenoisoquinolinone analogs, as described in United States Patent No. 8,119,654 to Jagtap et al.; (15) benzoxazole carboxamides, described in United States Patent No. 8,088,760 to Chu et al; (16) diazabenzo[de] anthracen-3-one compounds, described in United States Patent No. 8,058,075 to Xu et al.; (17) dihydropyridophthalazinones, described in United States Patent No. 8,012,976 to Wang et al., (18) substituted azaindoles, described in United States Patent No. 8,008,491 to Jiang et al.; (19) fused tricyclic compounds, described in United States Patent No. 7,956,064 to Chua et al.; (20) substituted 6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5*H*)-ones, described in United States Patent No. 7,928,105 to Gangloff et al.; and (21) thieno[2,3-c] isoquinolines, described in United States Patent No. 7,825,129, all of which patents are incorporated herein by this reference. Other PARP inhibitors are known in the art.

[0158] When the improvement is made by pharmacokinetic/pharmacodynamic monitoring, the pharmacokinetic/pharmacodynamic monitoring can be, but is not limited to a method selected from the group consisting of:

(a) multiple determinations of blood plasma levels; and

(b) multiple determinations of at least one metabolite in blood or urine.

[0159] Typically, determination of blood plasma levels or determination of at least one metabolite in blood or urine is carried out by immunoassays. Methods for performing immunoassays are well known in the art, and include radioimmunoassay, ELISA (enzyme-linked immunosorbent assay), competitive immunoassay, immunoassay employing lateral flow test strips, and other assay methods.

[0160] When the improvement is made by drug combination, the drug combination can be, but is not limited to, a drug combination selected from the group consisting of:

(a) use with topoisomerase inhibitors;

(b) use with fraudulent nucleosides;

(c) use with fraudulent nucleotides;

(d) use with thymidylate synthetase inhibitors;

(e) use with signal transduction inhibitors;

(f) use with cisplatin, oxaliplatin, or other platinum analogs;

(g) use with monofunctional alkylating agents;

(h) use with bifunctional alkylating agents;

(i) use with alkylating agents that damage DNA at a different place than does dianhydrogalactitol;

(j) use with anti-tubulin agents;

(k) use with antimetabolites;

(l) use with berberine;

(m) use with apigenin;

(n) use with amonafide;

(o) use with colchicine or analogs;

(p) use with genistein;

(q) use with etoposide;

(r) use with cytarabine;

(s) use with camptothecins

(t) use with vinca alkaloids;

(u) use with 5-fluorouracil;

(v) use with curcumin;

(w) use with NF-κB inhibitors;

(x) use with rosmarinic acid;

(y) use with mitoguazone;

(z) use with tetrandrine;

(aa) use with temozolomide;

(ab) use with VEGF inhibitors;

(ac) use with cancer vaccines;

(ad) use with EGFR inhibitors;

(ae) use with tyrosine kinase inhibitors;

(af) use with poly (ADP-ribose) polymerase (PARP) inhibitors; and

(ag) use with ALK inhibitors.

[0161] Topoisomerase inhibitors include, but are not limited to, irinotecan, topotecan, camptothecin, lamellarin D, amsacrine, etoposide, etoposide phosphate, teniposide, doxorubicin, and ICRF-193.

[0162] Fraudulent nucleosides include, but are not limited to, cytosine arabinoside, gemcitabine, and fludarabine; other fraudulent nucleosides are known in the art.

[0163] Fraudulent nucleotides include, but are not limited to, tenofovir disoproxil fumarate and adefovir dipivoxil; other fraudulent nucleotides are known in the art.

[0164] Thymidylate synthetase inhibitors include, but are not limited to, raltitrexed, pemetrexed, nolatrexed, ZD9331, GS7094L, fluorouracil, and BGC 945.

[0165] Signal transduction inhibitors are described in A.V. Lee et al., "New Mechanisms of Signal Transduction Inhibitor Action: Receptor Tyrosine Kinase Down-Regulation and Blockade of Signal Transactivation," Clin. Cancer Res. 9: 516s (2003), incorporated herein in its entirety by this reference.

[0166] Alkylating agents include, but are not limited to, Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bendamustine, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine (BCNU), Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)$_2$, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsulfam, ifosfamide, iproplatin, lomustine (CCNU), mafosfamide, melphalan, mitolactol, nimustine (ACNU), Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromustine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol, as described in United States Patent No. 7,446,122 by Chao et al., incorporated herein by this reference. Temozolomide, BCNU, CCNU, and ACNU all damage DNA at O^6 of guanine, whereas DAG cross-links at N^7); one alternative is therefore to use DAG in combination with an alkylating agent that damages DNA at a different place than DAG.

The alkylating agent can be a monofunctional alkylating agent or a bifunctional alkylating agent. Monofunctional alkylating agents include, but are not limited to, carmustine lomustine, temozolomide, and dacarbazine, as described in N. Kondo et al., "DNA Damage Induced by Alkylating Agents and Repair Pathways," J. Nucl. Acids doi:10.4061/2010/543531 (2010), incorporated herein by this reference; monofunctional alkylating agents also include such agents as methyl methanesulfonate, ethylmethanesulfonate, and N-methyl-N-nitrosoguanidine, as described in J.M. Walling & I.J. Stratford, "Chemosensitization by Monofunctional Alkylating Agents," Int. J. Radiat. Oncol. Biol. Phys. 12: 1397-1400 (1986), incorporated herein by this reference. Bifunctional alkylating agents include, but are not limited to, mechlorethamine, chlorambucil, cyclophosphamide, busulfan, nimustine, carmustine, lomustine, fotemustine, and bis-(2-chloroethyl) sulfide (N. Kondo et al. (2010), supra). One significant class of bifunctional alkylating agents includes alkylating agents that target O^6 of guanine in DNA. Another significant class of alkylating agents comprises cisplatin and other platinum-containing agents, including, but not limited to, cisplatin, carboplatin, iproplatin, oxaliplatin, tetraplatin, satraplatin, picoplatin, nedaplatin, and triplatin. These agents cause cross-linking of DNA, which then induces apoptosis. The combination with cisplatin, oxaliplatin, or other platinum-containing agents is a potential component of standard platinum doublet therapy. Additionally, the ability to be more than additive or synergistic is particularly significant with respect to the combination of a substituted hexitol derivative such as dianhydrogalactitol with cisplatin, oxaliplatin, or other platinum-containing chemotherapeutic agents, as well as other chemotherapeutic agents recited herein.

[0167] Anti-tubulin agents include, but are not limited to, vinca alkaloids, taxanes, podophyllotoxin, halichondrin B, and homohalichondrin B.

[0168] Antimetabolites include, but are not limited to: methotrexate, pemetrexed, 5-fluorouracil, capecitabine, cytarabine, gemcitabine, 6-mercaptopurine, and pentostatin, alanosine, AG2037 (Pfizer), 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrill-Dow DDFC, deazaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi

DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, N-(2′-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT and uricytin.

[0169] Berberine has antibiotic activity and prevents and suppresses the expression of pro-inflammatory cytokines and E-selectin, as well as increasing adiponectin expression.

[0170] Apigenin is a flavone that can reverse the adverse effects of cyclosporine and has chemoprotective activity, either alone or derivatized with a sugar.

[0171] Amonafide is a topoisomerase inhibitor and DNA intercalator that has anti-neoplastic activity.

[0172] Curcumin is believed to have anti-neoplastic, anti-inflammatory, antioxidant, anti-ischemic, anti-arthritic, and anti-amyloid properties and also has hepatoprotective activity.

[0173] NF-κB inhibitors include, but are not limited to, bortezomib.

[0174] Rosmarinic acid is a naturally-occurring phenolic antioxidant that also has anti-inflammatory activity.

[0175] Mitoguazone is an inhibitor of polyamine biosynthesis through competitive inhibition of *S*-adenosylmethionine decarboxylase.

[0176] Tetrandrine has the chemical structure 6,6′,7,12-tetramethoxy-2,2′-dimethyl-1 β-berbaman and is a calcium channel blocker that has anti-inflammatory, immunologic, and antiallergenic effects, as well as an anti-arrhythmic effect similar to that of quinidine. It has been isolated from *Stephania tetranda* and other Asian herbs.

[0177] VEGF inhibitors include bevacizumab (Avastin), which is a monoclonal antibody against VEGF, itraconazole, and suramin, as well as batimastat and marimastat, which are matrix metalloproteinase inhibitors, and cannabinoids and derivatives thereof.

[0178] Cancer vaccines are being developed. Typically, cancer vaccines are based on an immune response to a protein or proteins occurring in cancer cells that does not occur in normal cells. Cancer vaccines include Provenge for metastatic hormone-refractory prostate cancer, Oncophage for kidney cancer, CimaVax-EGF for lung cancer, MOBILAN, Neuvenge for Her2/neu expressing cancers such as breast cancer, colon cancer, bladder cancer, and ovarian cancer, Stimuvax for breast cancer, and others. Cancer vaccines are described in S. Pejawar-Gaddy & O. Finn, "Cancer Vaccines: Accomplishments and Challenges," Crit. Rev. Oncol. Hematol. 67: 93-102 (2008), incorporated herein by this reference.

[0179] The epidermal growth factor receptor (EGFR) exists on the cell surface of mammalian cells and is activated by binding of the receptor to its specific ligands, including, but not limited to epidermal growth factor and transforming growth factor α. Upon activation by binding to its growth factor ligands, EGFR undergoes a transition from an inactive monomeric form to an active homodimer, although preformed active dimers may exist before ligand binding. In addition to forming active homodimers after ligand binding, EGFR may pair with another member of the ErbB receptor family, such as ErbB2/Her2/neu, to create an activated heterodimer. There is also evidence that clusters of activated EGFRs form, although it is uncertain whether such clustering is important for activation itself or occurs subsequent to activation of individual dimers. EGFR dimerization stimulates its intracellular intrinsic protein-tyrosine kinase activity. As a result, autophosphorylation of several tyrosine residues in the carboxyl-terminal domain of EGFR occurs. These residues include Y992, Y1045, Y1068, Y1148, and Y1171. Such autophosphorylation elicits downstream activation and signaling by several other proteins that associate with the phosphorylated tyrosine residues through their own phosphotyrosine-binding SH2 domains. The signaling of these proteins that associate with the phosphorylated tyrosine residues through their own phosphotyrosine-binding SH2 domains can then initiate several signal transduction cascades and lead to DNA synthesis and cell proliferation. The kinase domain of EGFR can also cross-phosphorylate tyrosine residues of other receptors that it is aggregated with, and can itself be activated in that manner. EGFR is encoded by the *c-erbB1* proto-oncogene and has a molecular mass of 170 kDa. It is a transmembrane glycoprotein with a

cysteine-rich extracellular region, an intracellular domain containing an uninterrupted tyrosine kinase site, and multiple autophosphorylation sites clustered at the carboxyl-terminal tail as described above. The extracellular portion has been subdivided into four domains: domains I and III, which have 37% sequence identity, are cysteine-poor and conformationally contain the site for ligand (EGF and transforming growing factor α (TGFα) binding. Cysteine-rich domains II and IV contain *N*-linked glycosylation sites and disulfide bonds, which determine the tertiary conformation of the external domain of the protein molecule. In many human cell lines, TGFα expression has a strong correlation with EGFR overexpression, and therefore TGFα was considered to act in an autocrine manner, stimulating proliferation of the cells in which it is produced via activation of EGFR. Binding of a stimulatory ligand to the EGFR extracellular domain results in receptor dimerization and initiation of intracellular signal transduction, the first step of which is activation of the tyrosine kinase. The earliest consequence of kinase activation is the phosphorylation of its own tyrosine residues (autophosphorylation) as described above. This is followed by association with activation of signal transducers leading to mitogenesis. Mutations that lead to EGFR expression or overactivity have been associated with a number of malignancies, including glioblastoma multiforme. A specific mutation of EGFR known as EGFR Variant III has frequently been observed in glioblastoma (C.T. Kuan et al., "EGF Mutant Receptor VIII as a Molecular Target in Cancer Therapy," Endocr. Relat. Cancer 8: 83-96 (2001), incorporated herein by this reference). EGFR is considered an oncogene. Inhibitors of EGFR include, but are not limited to, erlotinib, gefitinib, lapatinib, lapatinib ditosylate, afatinib, canertinib, neratinib, CP-724714, WHI-P154, TAK-285, AST-1306, ARRY-334543, ARRY-380, AG-1478, tyrphostin 9, dacomitinib, desmethylerlotinib, OSI-420, AZD8931, AEE788, pelitinib, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035 HCl, BMS-599626, BIBW 2992, CI 1033, CP 724714, OSI 420, and vandetinib. Particularly preferred EGFR inhibitors include erlotinib, afatinib, and lapatinib.

[0180] Tyrosine kinase inhibitors include, but are not limited to, imatinib, gefitinib, erlotinib, sunitinib, sorafenib, foretinib, cederinib, axitinib, carbozantinib, BIBF1120, golvatinib, dovitinib, ZM 306416, ZM 323881 HCl, SAR 131675, semaxinib, telatinib, pazopanib, ponatinib, crenolanib, tivanitib, mubritinib, danusertib, brivanib,

fingolimod, saracatinib, rebastinib, quizartinib, tandutinib, amuvatinib, ibrutinib, fostamatinib, crizotinib, and linsitinib. Such tyrosine kinase inhibitors can inhibit tyrosine kinases associated with one or more of the following receptors: VEGFR, EGFR, PDGFR, c-Kit, c-Met, Her-2, FGFR, FLT-3, IGF-1R, ALK, c-RET, and Tie-2. As the activity of epidermal growth factor receptor (EGFR) involves the activity of a tyrosine kinase, the category of tyrosine kinase inhibitors overlaps with the category of EGFR inhibitors. A number of tyrosine kinase inhibitors inhibit the activity of both EGFR and at least one other tyrosine kinase. In general, tyrosine kinase inhibitors can operate by four different mechanisms: competition with adenosine triphosphate (ATP), used by the tyrosine kinase to carry out the phosphorylation reaction; competition with the substrate; competition with both ATP and the substrate; or allosteric inhibition. The activity of these inhibitors is disclosed in P. Yaish et al., "Blocking of EGF-Dependent Cell Proliferation by EGF Receptor Kinase Inhibitors," Science 242: 933-935 (1988); A. Gazit et al., "Tyrphostins. 2. Heterocyclic and α-Substituted Benzylidenemalononitrile Tyrphostins as Potent Inhibitors of EGF Receptor and ErbB2/neu Tyrosine Kinases," J. Med. Chem. 34: 1896-1907 (1991); N. Osherov et al., "Selective Inhibition of the Epidermal Growth Factor and HER2/neu Receptors by Tyrphostins," J. Biol. Chem. 268: 11134-11142 (1993); and A. Levitzki & E. Mishani, "Tyrphostins and Other Tyrosine Kinase Inhibitors," Annu. Rev. Biochem. 75: 93-109 (2006), all of which are incorporated herein by this reference.

[0181] ALK inhibitors act on tumors with variations of anaplastic lymphoma kinase (ALK) such as an EML4-ALK translocation. ALK inhibitors include, but are not limited to: crizotinib (3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine); AP26113 ((2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)dimethylphosphine oxide); ASP-3026 (N2-[2-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]phenyl]-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-1,3,5-triazine-2,4-diamine); alectinib (9-ethyl-6,6-dimethyl-8-(4-morpholin-4-ylpiperidin-1-yl)-11-oxo-5H-benzo[b]carbazole-3-carbonitrile); NMS-E628 (*N*-(5-(3,5-difluorobenzyl)-1*H*-indazol-3-yl)-4-(4-methylpiperazin-1-yl)-2-((tetrahydro-2*H*-pyran-4-yl)amino)benzamide); ceritinib; PF-06363922; TSR-011; CEP-37440 (2-[[5-Chloro-2-[[(6S)-6-[4-(2-

hydroxyethyl)piperazin-1-yl]-1-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-yl]amino]pyrimidin-4-yl]amino]-N-methyl-benzamide); and X-396 (*R*)-6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-*N*-(4-(4-methylpiperazine-1-carbonyl)phenyl)pyridazine-3-carboxamide).

[0182] These additional agents described above can be used in drug combinations together with the substituted hexitol derivative for treatment of either NSCLC or ovarian cancer. The additional agent to be included is one that is either known to possess activity against the type of cancer being treated (NSCLC or ovarian cancer), is structurally related to a compound or a class of compounds known to possess activity against the type of cancer being treated, or is known to modulate a pathway for which modulation has been shown to be effective against the type of cancer being treated. As used herein, the term "modulation" can include either activation or inhibition of the pathway involved, but typically refers to inhibition of the pathway.

[0183] When methods according to the present invention are intended for treatment of ovarian cancer, drug combinations can include the use of a substituted hexitol derivative as described above together with an additional agent that possesses anti-neoplastic activity against ovarian tumors. Such additional agents include, but are not limited to, paclitaxel, docetaxel, cisplatin, carboplatin, topotecan, gemcitabine, bleomycin, etoposide, doxorubicin (which can be used in a pegylated liposomal form), tamoxifen, letrozole, olaparib, selumetinib, mTOR inhibitors, PI3 kinase inhibitors, and trichostatin A.

[0184] Additional agents that possess anti-neoplastic activity against NSCLC are known in the art. These additional agents can be included in drug combinations according to the present invention in a therapeutically effective quantity together with a therapeutically effective quantity of a substituted hexitol derivative as described above. One or more than one of these additional agents can be used. These additional agents can be used together with one or more of the agents as described above for activity against NSCLC in drug combinations including a substituted hexitol derivative such as dianhydrogalactitol or diacetyldianhydrogalactitol. The agents are those collectively referred to herein as "Additional Secondary Agents with Activity Against NSCLC."

[0185] Additional agents that possess anti-neoplastic activity against ovarian cancer are known in the art. These additional agents can be included in drug combinations according to the present invention in a therapeutically effective quantity together with a therapeutically effective quantity of a substituted hexitol derivative as described above. One or more than one of these additional agents can be used. These additional agents can be used together with one or more of the agents as described above for activity against ovarian cancer in drug combinations including a substituted hexitol derivative such as dianhydrogalactitol or diacetyldianhydrogalactitol. The agents are those collectively referred to herein as "Additional Secondary Agents with Activity Against Ovarian Cancer."

[0186] When the improvement is made by chemosensitization, the chemosensitization can comprise, but is not limited to, the use of a substituted hexitol derivative as a chemosensitizer in combination with an agent selected from the group consisting of:

(a) topoisomerase inhibitors;
(b) fraudulent nucleosides;
(c) fraudulent nucleotides;
(d) thymidylate synthetase inhibitors;
(e) signal transduction inhibitors;
(f) cisplatin, oxaliplatin, or another platinum analog;
(g) alkylating agents;
(h) anti-tubulin agents;
(i) antimetabolites;
(j) berberine;
(k) apigenin;
(l) amonafide;
(m) colchicine or analogs;
(n) genistein;
(o) etoposide;
(p) cytarabine;
(q) camptothecins;

(r) vinca alkaloids;
(s) topoisomerase inhibitors;
(t) 5-fluorouracil;
(u) curcumin;
(v) NF-κB inhibitors;
(w) rosmarinic acid;
(x) mitoguazone;
(y) tetrandrine;
(z) a tyrosine kinase inhibitor;
(aa) an inhibitor of EGFR; and
(ab) an inhibitor of PARP.

[0187] When the improvement is made by chemopotentiation, the chemopotentiation can comprise, but is not limited to, the use of a substituted hexitol derivative as a chemopotentiator in combination with an agent selected from the group consisting of:

(a) topoisomerase inhibitors;
(b) fraudulent nucleosides;
(c) fraudulent nucleotides;
(d) thymidylate synthetase inhibitors;
(e) signal transduction inhibitors;
(f) cisplatin, oxaliplatin, or another platinum analog;
(g) alkylating agents;
(h) anti-tubulin agents;
(i) antimetabolites;
(j) berberine;
(k) apigenin;
(l) amonafide;
(m) colchicine or analogs;
(n) genistein;
(o) etoposide;
(p) cytarabine;

(q) camptothecins;

(r) vinca alkaloids;

(s) 5-fluorouracil;

(t) curcumin;

(u) NF-κB inhibitors;

(v) rosmarinic acid;

(w) mitoguazone;

(x) tetrandrine;

(y) a tyrosine kinase inhibitor;

(z) an inhibitor of EGFR; and

(aa) an inhibitor of PARP.

[0188] When the improvement is made by post-treatment management, the post-treatment management can be, but is not limited to, a method selected from the group consisting of:

(a) a therapy associated with pain management;

(b) administration of an anti-emetic;

(c) an anti-nausea therapy;

(d) administration of an anti-inflammatory agent;

(e) administration of an anti-pyretic agent; and

(f) administration of an immune stimulant.

[0189] When the improvement is made by alternative medicine/post-treatment support, the alternative medicine/post-treatment support can be, but is not limited to, a method selected from the group consisting of:

(a) hypnosis;

(b) acupuncture;

(c) meditation;

(d) a herbal medication created either synthetically or through extraction; and

(e) applied kinesiology.

[0190] In one alternative, when the method is a herbal medication created either synthetically or through extraction, the herbal medication created either synthetically or through extraction can be selected from the group consisting of:

(a) a NF-κB inhibitor;

(b) a natural anti-inflammatory;

(c) an immunostimulant;

(d) an antimicrobial; and

(e) a flavonoid, isoflavone, or flavone.

[0191] When the herbal medication created either synthetically or through extraction is a NF-κB inhibitor, the NF-κB inhibitor can be selected from the group consisting of parthenolide, curcumin, and rosmarinic acid. When the herbal medication created either synthetically or through extraction is a natural anti-inflammatory, the natural anti-inflammatory can be selected from the group consisting of rhein and parthenolide. When the herbal medication created either synthetically or through extraction is an immunostimulant, the immunostimulant can be a product found in or isolated from Echinacea. When the herbal medication created either synthetically or through extraction is an anti-microbial, the anti-microbial can be berberine. When the herbal medication created either synthetically or through extraction is a flavonoid or flavone, the flavonoid, isoflavone, or flavone can be selected from the group consisting of apigenin, genistein, apigenenin, genistein, genistin, 6″-O-malonylgenistin, 6″-O-acetylgenistin, daidzein, daidzin, 6″-O-malonyldaidzin, 6″-O-acetylgenistin, glycitein, glycitin, 6″-O-malonylglycitin, and 6-O-acetylglycitin.

[0192] When the improvement is made by a bulk drug product improvement, the bulk drug product improvement can be, but is not limited to, a bulk drug product improvement selected from the group consisting of:

(a) salt formation;

(b) preparation as a homogeneous crystal structure;

(c) preparation as a pure isomer;

(d) increased purity;

(e) preparation with lower residual solvent content; and

(f) preparation with lower residual heavy metal content.

[0193] When the improvement is made by use of a diluent, the diluent can be, but is not limited to, a diluent selected from the group consisting of:

(a) an emulsion;
(b) dimethylsulfoxide (DMSO);
(c) N-methylformamide (NMF)
(d) DMF;
(e) ethanol;
(f) benzyl alcohol;
(g) dextrose-containing water for injection;
(h) Cremophor;
(i) cyclodextrin; and
(j) PEG.

[0194] When the improvement is made by use of a solvent system, the solvent system can be, but is not limited to, a solvent system selected from the group consisting of:

(a) an emulsion;
(b) dimethylsulfoxide (DMSO);
(c) N-methylformamide (NMF)
(d) DMF;
(e) ethanol;
(f) benzyl alcohol;
(g) dextrose-containing water for injection;
(h) Cremophor;
(i) cyclodextrin; and
(j) PEG.

[0195] When the improvement is made by use of an excipient, the excipient can be, but is not limited to, an excipient selected from the group consisting of:

(a) mannitol;
(b) albumin;
(c) EDTA;
(d) sodium bisulfite;

(e) benzyl alcohol;

(f) a carbonate buffer; and

(g) a phosphate buffer.

[0196] When the improvement is made by use of a dosage form, the dosage form can be, but is not limited to, a dosage form selected from the group consisting of:

(a) tablets;

(b) capsules;

(c) topical gels;

(d) topical creams;

(e) patches;

(f) suppositories; and

(g) lyophilized dosage fills.

[0197] Formulation of pharmaceutical compositions in tablets, capsules, and topical gels, topical creams or suppositories is well known in the art and is described, for example, in United States Patent Application Publication No. 2004/0023290 by Griffin et al., incorporated herein by this reference.

[0198] Formulation of pharmaceutical compositions as patches such as transdermal patches is well known in the art and is described, for example, in United States Patent No. 7,728,042 to Eros et al., incorporated herein by this reference.

[0199] Lyophilized dosage fills are also well known in the art. One general method for the preparation of such lyophilized dosage fills, applicable to dianhydrogalactitol and derivatives thereof and to diacetyldianhydrogalactitol and derivatives thereof, comprises the following steps:

(1) Dissolve the drug in water for injection precooled to below 10° C. Dilute to final volume with cold water for injection to yield a 40 mg/mL solution.

(2) Filter the bulk solution through an 0.2-μm filter into a receiving container under aseptic conditions. The formulation and filtration should be completed in 1 hour.

(3) Fill nominal 1.0 mL filtered solution into sterilized glass vials in a controlled target range under aseptic conditions.

(4) After the filling, all vials are placed with rubber stoppers inserted in the "lyophilization position" and loaded in the prechilled lyophilizer. For the lyophilizer, shelf temperature is set at +5° C and held for 1 hour; shelf temperature is then adjusted to -5° C and held for one hour, and the condenser, set to -60° C, turned on.

(5) The vials are then frozen to 30° C or below and held for no less than 3 hours, typically 4 hours.

(6) Vacuum is then turned on, the shelf temperature is adjusted to -5° C, and primary drying is performed for 8 hours; the shelf temperature is again adjusted to -5° C and drying is carried out for at least 5 hours.

(7) Secondary drying is started after the condenser (set at -60° C) and vacuum are turned on. In secondary drying, the shelf temperature is controlled at +5° C for 1 to 3 hours, typically 1.5 hours, then at 25°C for 1 to 3 hours, typically 1.5 hours, and finally at 35-40° C for at least 5 hours, typically for 9 hours, or until the product is completely dried.

(8) Break the vacuum with filtered inert gas (e.g., nitrogen). Stopper the vials in the lyophilizer.

(9) Vials are removed from the lyophilizer chamber and sealed with aluminum flip-off seals. All vials are visually inspected and labeled with approved labels.

[0200] When the improvement is made by use of dosage kits and packaging, the dosage kits and packaging can be, but are not limited to, dosage kits and packaging selected from the group consisting of the use of amber vials to protect from light and the use of stoppers with specialized coatings to improve shelf-life stability.

[0201] When the improvement is made by use of a drug delivery system, the drug delivery system can be, but is not limited to, a drug delivery system selected from the group consisting of:

(a) nanocrystals;

(b) bioerodible polymers;

(c) liposomes;

(d) slow release injectable gels; and

(e) microspheres.

[0202] Nanocrystals are described in United States Patent No. 7,101,576 to Hovey et al., incorporated herein by this reference.

[0203] Bioerodible polymers are described in United States Patent No. 7,318,931 to Okumu et al., incorporated herein by this reference. A bioerodible polymer decomposes when placed inside an organism, as measured by a decline in the molecular weight of the polymer over time. Polymer molecular weights can be determined by a variety of methods including size exclusion chromatography (SEC), and are generally expressed as weight averages or number averages. A polymer is bioerodible if, when in phosphate buffered saline (PBS) of pH 7.4 and a temperature of 37° C, its weight-average molecular weight is reduced by at least 25% over a period of 6 months as measured by SEC. Useful bioerodible polymers include polyesters, such as poly(caprolactone), poly(glycolic acid), poly(lactic acid), and poly(hydroxybutryate); polyanhydrides, such as poly(adipic anhydride) and poly(maleic anhydride); polydioxanone; polyamines; polyamides; polyurethanes; polyesteramides; polyorthoesters; polyacetals; polyketals; polycarbonates; polyorthocarbonates; polyphosphazenes; poly(malic acid); poly(amino acids); polyvinylpyrrolidone; poly(methyl vinyl ether); poly(alkylene oxalate); poly(alkylene succinate); polyhydroxycellulose; chitin; chitosan; and copolymers and mixtures thereof.

[0204] Liposomes are well known as drug delivery vehicles. Liposome preparation is described in European Patent Application Publication No. EP 1332755 by Weng et al., incorporated herein by this reference.

[0205] Slow release injectable gels are known in the art and are described, for example, in B. Jeong et al., "Drug Release from Biodegradable Injectable Thermosensitive Hydrogel of PEG-PLGA-PEG Triblock Copolymers," J. Controlled Release 63: 155-163 (2000), incorporated herein by this reference.

[0206] The use of microspheres for drug delivery is known in the art and is described, for example, in H. Okada & H. Taguchi, "Biodegradable Microspheres in Drug Delivery," Crit. Rev. Ther. Drug Carrier Sys. 12: 1-99 (1995), incorporated herein by this reference.

[0207] When the improvement is made by use of a drug conjugate form, the drug conjugate form can be, but is not limited to, a drug conjugate form selected from the group consisting of:

(a) a polymer system;
(b) polylactides;
(c) polyglycolides;
(d) amino acids;
(e) peptides; and
(f) multivalent linkers.

[0208] Polylactide conjugates are well known in the art and are described, for example, in R. Tong & C. Cheng, "Controlled Synthesis of Camptothecin-Polylactide Conjugates and Nanoconjugates," Bioconjugate Chem. 21: 111-121 (2010), incorporated by this reference.

[0209] Polyglycolide conjugates are also well known in the art and are described, for example, in PCT Patent Application Publication No. WO 2003/070823 by Elmaleh et al., incorporated herein by this reference.

[0210] Multivalent linkers are known in the art and are described, for example, in United States Patent Application Publication No. 2007/0207952 by Silva et al., incorporated herein by this reference. For example, multivalent linkers can contain a thiophilic group for reaction with a reactive cysteine, and multiple nucleophilic groups (such as NH or OH) or electrophilic groups (such as activated esters) that permit attachment of a plurality of biologically active moieties to the linker.

[0211] Suitable reagents for cross-linking many combinations of functional groups are known in the art. For example, electrophilic groups can react with many functional groups, including those present in proteins or polypeptides. Various combinations of reactive amino acids and electrophiles are known in the art and can be used. For example, N-terminal cysteines, containing thiol groups, can be reacted with halogens or maleimides. Thiol groups are known to have reactivity with a large number of coupling agents, such as alkyl halides, haloacetyl derivatives, maleimides, aziridines, acryloyl derivatives, arylating agents such as aryl halides, and others. These are described in G. T. Hermanson, "Bioconjugate Techniques" (Academic Press, San

Diego, 1996), pp. 146-150, incorporated herein by this reference. The reactivity of the cysteine residues can be optimized by appropriate selection of the neighboring amino acid residues. For example, a histidine residue adjacent to the cysteine residue will increase the reactivity of the cysteine residue. Other combinations of reactive amino acids and electrophilic reagents are known in the art. For example, maleimides can react with amino groups, such as the ε-amino group of the side chain of lysine, particularly at higher pH ranges. Aryl halides can also react with such amino groups. Haloacetyl derivatives can react with the imidazolyl side chain nitrogens of histidine, the thioether group of the side chain of methionine, and the ε-amino group of the side chain of lysine. Many other electrophilic reagents are known that will react with the ε-amino group of the side chain of lysine, including, but not limited to, isothiocyanates, isocyanates, acyl azides, N-hydroxysuccinimide esters, sulfonyl chlorides, epoxides, oxiranes, carbonates, imidoesters, carbodiimides, and anhydrides. These are described in G.T. Hermanson, “Bioconjugate Techniques” (Academic Press, San Diego, 1996), pp. 137-146, incorporated herein by this reference. Additionally, electrophilic reagents are known that will react with carboxylate side chains such as those of aspartate and glutamate, such as diazoalkanes and diazoacetyl compounds, carbonydilmidazole, and carbodiimides. These are described in G. T. Hermanson, "Bioconjugate Techniques" (Academic Press, San Diego, 1996), pp. 152-154, incorporated herein by this reference. Furthermore, electrophilic reagents are known that will react with hydroxyl groups such as those in the side chains of serine and threonine, including reactive haloalkane derivatives. These are described in G. T. Hermanson, “Bioconjugate Techniques” (Academic Press, San Diego, 1996), pp. 154-158, incorporated herein by this reference. In another alternative embodiment, the relative positions of electrophile and nucleophile (i.e., a molecule reactive with an electrophile) are reversed so that the protein has an amino acid residue with an electrophilic group that is reactive with a nucleophile and the targeting molecule includes therein a nucleophilic group. This includes the reaction of aldehydes (the electrophile) with hydroxylamine (the nucleophile), described above, but is more general than that reaction; other groups can be used as electrophile and nucleophile. Suitable groups are well known in organic chemistry and need not be described further in detail.

[0212] Additional combinations of reactive groups for cross-linking are known in the art. For example, amino groups can be reacted with isothiocyanates, isocyanates, acyl azides, N-hydroxysuccinimide (NHS) esters, sulfonyl chlorides, aldehydes, glyoxals, epoxides, oxiranes, carbonates, alkylating agents, imidoesters, carbodiimides, and anhydrides. Thiol groups can be reacted with haloacetyl or alkyl halide derivatives, maleimides, aziridines, acryloyl derivatives, acylating agents, or other thiol groups by way of oxidation and the formation of mixed disulfides. Carboxy groups can be reacted with diazoalkanes, diazoacetyl compounds, carbonyldiimidazole, carbodiimides. Hydroxyl groups can be reacted with epoxides, oxiranes, carbonyldiimidazole, N,N′-disuccinimidyl carbonate, N-hydroxysuccinimidyl chloroformate, periodate (for oxidation), alkyl halogens, or isocyanates. Aldehyde and ketone groups can react with hydrazines, reagents forming Schiff bases, and other groups in reductive amination reactions or Mannich condensation reactions. Still other reactions suitable for cross-linking reactions are known in the art. Such cross-linking reagents and reactions are described in G.T. Hermanson, "Bioconjugate Techniques" (Academic Press, San Diego, 1996), incorporated herein by this reference.

[0213] When the improvement is made by use of a compound analog, the compound analog can be, but is not limited to, a compound analog selected from the group consisting of:

(a) alteration of side chains to increase or decrease lipophilicity;

(b) addition of an additional chemical functionality to alter a property selected from the group consisting of reactivity, electron affinity, and binding capacity; and

(c) alteration of salt form.

[0214] When the improvement is made by use of a prodrug system, the prodrug system can be, but is not limited to, a prodrug system selected from the group consisting of:

(a) the use of enzyme sensitive esters;

(b) the use of dimers;

(c) the use of Schiff bases;

(d) the use of pyridoxal complexes; and

(e) the use of caffeine complexes.

[0215] The use of prodrug systems is described in T. Järvinen et al., "Design and Pharmaceutical Applications of Prodrugs" in Drug Discovery Handbook (S.C. Gad, ed., Wiley-Interscience, Hoboken, NJ, 2005), ch. 17, pp. 733-796, incorporated herein by this reference. This publication describes the use of enzyme sensitive esters as prodrugs. The use of dimers as prodrugs is described in United States Patent No. 7,879,896 to Allegretti et al., incorporated herein by this reference. The use of peptides in prodrugs is described in S. Prasad et al., "Delivering Multiple Anticancer Peptides as a Single Prodrug Using Lysyl-Lysine as a Facile Linker," J. Peptide Sci. 13: 458-467 (2007), incorporated herein by this reference. The use of Schiff bases as prodrugs is described in United States Patent No. 7,619,005 to Epstein et al., incorporated herein by this reference. The use of caffeine complexes as prodrugs is described in United States Patent No. 6,443,898 to Unger et al., incorporated herein by this reference.

[0216] When the improvement is made by use of a multiple drug system, the multiple drug system can be, but is not limited to, a multiple drug system selected from the group consisting of:

(a) use of multi-drug resistance inhibitors;

(b) use of specific drug resistance inhibitors;

(c) use of specific inhibitors of selective enzymes;

(d) use of signal transduction inhibitors;

(e) use of repair inhibition; and

(f) use of topoisomerase inhibitors with non-overlapping side effects.

[0217] Multi-drug resistance inhibitors are described in United States Patent No. 6,011,069 to Inomata et al., incorporated herein by this reference.

[0218] Specific drug resistance inhibitors are described in T. Hideshima et al., "The Proteasome Inhibitor PS-341 Inhibits Growth, Induces Apoptosis, and Overcomes Drug Resistance in Human Multiple Myeloma Cells," Cancer Res. 61: 3071-3076 (2001), incorporated herein by this reference.

[0219] Repair inhibition is described in N.M. Martin, "DNA Repair Inhibition and Cancer Therapy," J. Photochem. Photobiol. B 63: 162-170 (2001), incorporated herein by this reference.

[0220] When the improvement is made by biotherapeutic enhancement, the biotherapeutic enhancement can be performed by use in combination as sensitizers/potentiators with a therapeutic agent or technique that can be, but is not limited to, a therapeutic agent or technique selected from the group consisting of:

(a) cytokines;
(b) lymphokines;
(c) therapeutic antibodies;
(d) antisense therapies;
(e) gene therapies;
(f) ribozymes;
(g) RNA interference; and
(h) vaccines.

[0221] Antisense therapies are described, for example, in B. Weiss et al., "Antisense RNA Gene Therapy for Studying and Modulating Biological Processes," Cell. Mol. Life Sci. 55: 334-358 (1999), incorporated herein by this reference.

[0222] Ribozymes are described, for example, in S. Pascolo, "RNA-Based Therapies" in Drug Discovery Handbook (S.C. Gad, ed., Wiley-Interscience, Hoboken, NJ, 2005), ch.27, pp. 1273-1278, incorporated herein by this reference.

[0223] RNA interference is described, for example, in S. Pascolo, "RNA-Based Therapies" in Drug Discovery Handbook (S.C. Gad, ed., Wiley-Interscience, Hoboken, NJ, 2005), ch.27, pp. 1278-1283, incorporated herein by this reference.

[0224] As described above, typically, cancer vaccines are based on an immune response to a protein or proteins occurring in cancer cells that does not occur in normal cells. Cancer vaccines include Provenge for metastatic hormone-refractory prostate cancer, Oncophage for kidney cancer, CimaVax-EGF for lung cancer, MOBILAN, Neuvenge for Her2/neu expressing cancers such as breast cancer, colon cancer, bladder cancer, and ovarian cancer, Stimuvax for breast cancer, and others. Cancer vaccines are described in S. Pejawar-Gaddy & O. Finn (2008), supra.

[0225] When the biotherapeutic enhancement is use in combination as sensitizers/potentiators with a therapeutic antibody, the therapeutic antibody can be, but is not limited to, a therapeutic antibody selected from the group consisting of bevacizumab (Avastin), rituximab (Rituxan), trastuzumab (Herceptin), and cetuximab (Erbitux).

[0226] When the improvement is made by use of biotherapeutic resistance modulation, the biotherapeutic resistance modulation can be, but is not limited to, use against NSCLC resistant to a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;
(b) cytokines;
(c) lymphokines;
(d) therapeutic antibodies;
(e) antisense therapies;
(f) gene therapies;
(g) ribozymes;
(h) RNA interference; and
(i) vaccines.

[0227] When the biotherapeutic resistance modulation is use against tumors resistant to therapeutic antibodies, the therapeutic antibody can be, but is not limited to, a therapeutic antibody selected from the group consisting of bevacizumab (Avastin), rituximab (Rituxan), trastuzumab (Herceptin), and cetuximab (Erbitux).

[0228] When the improvement is made by radiation therapy enhancement, the radiation therapy enhancement can be, but is not limited to, a radiation therapy enhancement agent or technique selected from the group consisting of:

(a) hypoxic cell sensitizers;
(b) radiation sensitizers/protectors;
(c) photosensitizers;
(d) radiation repair inhibitors;
(e) thiol depleters;
(f) vaso-targeted agents;

(g) DNA repair inhibitors;
(h) radioactive seeds;
(i) radionuclides;
(j) radiolabeled antibodies; and
(k) brachytherapy.

[0229] A substituted hexitol derivative such as dianhydrogalactitol can be used in combination with radiation for the treatment of NSCLC or for the treatment of ovarian cancer.

[0230] Hypoxic cell sensitizers are described in C.C. Ling et al., "The Effect of Hypoxic Cell Sensitizers at Different Irradiation Dose Rates," Radiation Res. 109: 396-406 (1987), incorporated herein by this reference. Radiation sensitizers are described in T.S. Lawrence, "Radiation Sensitizers and Targeted Therapies," Oncology 17 (Suppl. 13) 23-28 (2003), incorporated herein by this reference. Radiation protectors are described in S.B. Vuyyuri et al., "Evaluation of D-Methionine as a Novel Oral Radiation Protector for Prevention of Mucositis," Clin. Cancer Res. 14: 2161-2170 (2008), incorporated herein by this reference. Photosensitizers are described in R.R. Allison & C.H. Sibata, "Oncologic Photodynamic Therapy Photosensitizers: A Clinical Review," Photodiagnosis Photodynamic Ther. 7: 61-75 (2010), incorporated herein by this reference. Radiation repair inhibitors and DNA repair inhibitors are described in M. Hingorani et al., "Evaluation of Repair of Radiation-Induced DNA Damage Enhances Expression from Replication-Defective Adenoviral Vectors," Cancer Res. 68: 9771-9778 (2008), incorporated herein by this reference. Thiol depleters are described in K.D. Held et al., "Postirradiation Sensitization of Mammalian Cells by the Thiol-Depleting Agent Dimethyl Fumarate," Radiation Res. 127: 75-80 (1991), incorporated herein by this reference. Vaso-targeted agents are described in A.L. Seynhaeve et al., "Tumor Necrosis Factor α Mediates Homogeneous Distribution of Liposomes in Murine Melanoma that Contributes to a Better Tumor Response," Cancer Res. 67: 9455-9462 (2007). As described above, radiation therapy is employed for the treatment of NSCLC, so radiation therapy enhancement is significant for this malignancy.

[0231] When the improvement is by use of a novel mechanism of action, the novel mechanism of action can be, but is not limited to, a novel mechanism of action

that is a therapeutic interaction with a target or mechanism selected from the group consisting of:

(a) inhibitors of poly-ADP ribose polymerase;
(b) agents that affect vasculature or vasodilation;
(c) oncogenic targeted agents;
(d) signal transduction inhibitors;
(e) EGFR inhibition;
(f) protein kinase C inhibition;
(g) phospholipase C downregulation;
(h) Jun downregulation;
(i) histone genes;
(j) VEGF;
(k) ornithine decarboxylase;
(l) ubiquitin C;
(m) Jun D;
(n) v-Jun;
(o) GPCRs;
(p) protein kinase A;
(q) protein kinases other than protein kinase A;
(r) prostate specific genes;
(s) telomerase;
(t) histone deacetylase; and
(u) tyrosine kinase inhibitors.

[0232] EGFR inhibition is described in G. Giaccone & J.A. Rodriguez, "EGFR Inhibitors: What Have We Learned from the Treatment of Lung Cancer," Nat. Clin. Pract. Oncol. 11: 554-561 (2005), incorporated herein by this reference. Protein kinase C inhibition is described in H.C. Swannie & S.B. Kaye, "Protein Kinase C Inhibitors," Curr. Oncol. Rep. 4: 37-46 (2002), incorporated herein by this reference. Phospholipase C downregulation is described in A.M. Martelli et al., "Phosphoinositide Signaling in Nuclei of Friend Cells: Phospholipase C β Downregulation Is Related to Cell Differentiation," Cancer Res. 54: 2536-2540 (1994), incorporated herein by this

reference. Downregulation of Jun (specifically, c-Jun) is described in A. A. P. Zada et al., "Downregulation of c-Jun Expression and Cell Cycle Regulatory Molecules in Acute Myeloid Leukemia Cells Upon CD44 Ligation," Oncogene 22: 2296-2308 (2003), incorporated herein by this reference. The role of histone genes as a target for therapeutic intervention is described in B. Calabretta et al., "Altered Expression of G1-Specific Genes in Human Malignant Myeloid Cells," Proc. Natl. Acad. Sci. USA 83: 1495-1498 (1986). The role of VEGF as a target for therapeutic intervention is described in A. Zielke et al., "VEGF-Mediated Angiogenesis of Human Pheochromocytomas Is Associated to Malignancy and Inhibited by anti-VEGF Antibodies in Experimental Tumors," Surgery 132: 1056-1063 (2002), incorporated herein by this reference. The role of ornithine decarboxylase as a target for therapeutic intervention is described in J.A. Nilsson et al., "Targeting Ornithine Decarboxylase in Myc-Induced Lymphomagenesis Prevents Tumor Formation," Cancer Cell 7: 433-444 (2005), incorporated herein by this reference. The role of ubiquitin C as a target for therapeutic intervention is described in C. Aghajanian et al., "A Phase I Trial of the Novel Proteasome Inhibitor PS341 in Advanced Solid Tumor Malignancies," Clin. Cancer Res. 8: 2505-2511 (2002), incorporated herein by this reference. The role of Jun D as a target for therapeutic intervention is described in M.M. Caffarel et al., "JunD Is Involved in the Antiproliferative Effect of Δ^9-Tetrahydrocannibinol on Human Breast Cancer Cells," Oncogene 27: 5033-5044 (2008), incorporated herein by this reference. The role of v-Jun as a target for therapeutic intervention is described in M. Gao et al., "Differential and Antagonistic Effects of v-Jun and c-Jun," Cancer Res. 56: 4229-4235 (1996), incorporated herein by this reference. The role of protein kinase A as a target for therapeutic intervention is described in P.C. Gordge et al., "Elevation of Protein Kinase A and Protein Kinase C in Malignant as Compared With Normal Breast Tissue," Eur. J. Cancer 12: 2120-2126 (1996), incorporated herein by this reference. The role of telomerase as a target for therapeutic intervention is described in E.K. Parkinson et al., "Telomerase as a Novel and Potentially Selective Target for Cancer Chemotherapy," Ann. Med. 35: 466-475 (2003), incorporated herein by this reference. The role of histone deacetylase as a target for therapeutic intervention is described in A. Melnick &

J.D. Licht, "Histone Deacetylases as Therapeutic Targets in Hematologic Malignancies," Curr. Opin. Hematol. 9: 322-332 (2002), incorporated herein by this reference.

[0233] When the improvement is made by use of selective target cell population therapeutics, the use of selective target cell population therapeutics can be, but is not limited to, a use selected from the group consisting of:

(a) use against radiation sensitive cells;

(b) use against radiation resistant cells; and

(c) use against energy depleted cells.

[0234] The improvement can also be made by use of a substituted hexitol derivative in combination with ionizing radiation.

[0235] When the improvement is made by use of an agent that counteracts myelosuppression, the agent that counteracts myelosuppression can be, but is not limited to, a dithiocarbamate.

[0236] United States Patent No. 5,035,878 to Borch et al., incorporated herein by this reference, discloses dithiocarbamates for treatment of myelosuppression; the dithiocarbamates are compounds of the formula $R^1R^2NCS(S)M$ or R^1R^2NCSS-$SC(S)NR^3R^4$, wherein R^1, R^2, R^3, and R^4 are the same or different, and R^1, R^2, R^3, and R^4 are aliphatic, cycloaliphatic, or heterocycloaliphatic groups that are unsubstituted or substituted by hydroxyl; or wherein one of R^1 and R^2 and one of R^3 and R^4 can be hydrogen; or wherein R^1, R^2, R^3, and R^4 taken together with the nitrogen atom upon which the pair of R groups is substituted, can be a 5-membered or 6-membered N-heterocyclic ring which is aliphatic or aliphatic interrupted by a ring oxygen or a second ring nitrogen, and M is hydrogen or one equivalent or a pharmaceutically acceptable cation, in which case the rest of the molecule is negatively charged.

[0237] United States Patent No. 5,294,430 to Borch et al., incorporated herein by this reference, discloses additional dithiocarbamates for treatment of myelosuppression. In general, these are compounds of Formula (D-I):

(D-I)

wherein:

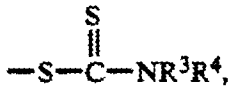
(i) R^1 and R^2 are the same or different C_1-C_6 alkyl groups, C_3-C_6 cycloalkyl groups, or C_5-C_6 heterocycloalkyl groups; or

(ii) one of R^1 and R^2, but not both, can be H; or

(iii) R^1 and R^2 taken together with the nitrogen atom can be a 5-membered or 6-membered N-heterocyclic ring which is aliphatic or aliphatic interrupted by a ring oxygen or a second ring nitrogen; and

(iv) M is hydrogen or one equivalent of a pharmaceutically acceptable cation, in which case the rest of the molecule is negatively charged; or

(v) M is a moiety of Formula (D-II):



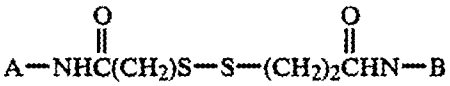
(D-II)

wherein R^3 and R^4 are defined in the same manner as R^1 and R^2. Where the group defined by Formula (D-I) is an anion, the cation can be an ammonium cation or can be derived from a monovalent or divalent metal such as an alkali metal or an alkaline earth metal, such as Na^+, K^+, or Zn^{+2}. In the case of the dithiocarbamic acids, the group defined by Formula (D-I) is linked to an ionizable hydrogen atom; typically, the hydrogen atom will dissociate at a pH above about 5.0. Among dithiocarbamates that can be used are: N-methyl,N-ethyldithiocarbamates, hexamethylenedithiocarbamic acid, sodium di(β-hydroxyethyl)dithiocarbamate, various dipropyl, dibutyl and diamyl dithiocarbamates, sodium N-methyl,N-cyclobutylmethyl dithiocarbamate, sodium N-allyl-N-cyclopropylmethyldithiocarbamate, cyclohexylamyldithiocarbamates, dibenzyl-dithiocarbamates, sodium dimethylene-dithiocarbamate, various pentamethylene dithiocarbamate salts, sodium pyrrolidine-N-carbodithioate, sodium piperidine-N-carbodithioate, sodium morpholine-N-carbo-dithioate, α-furfuryl dithiocarbamates and imidazoline dithiocarbamates. Another alternative is a compound where R^1 of Formula (D-I) is a hydroxy-substituted or, preferably, a (bis to penta) polyhydroxy-substituted lower alkyl group having up to 6 carbon atoms. For example, R^1 can be HO-CH_2-CHOH-CHOH-CHOH-CHOH-CH_2 -. In such compounds, R^2 can be H or lower alkyl

(unsubstituted or substituted with one or more hydroxyl groups). Steric problems can be minimized when R^2 is H, methyl, or ethyl. Accordingly, a particularly preferred compound of this type is an N-methyl-glucamine dithiocarbamate salt, the most preferred cations of these salts being sodium or potassium. Other preferred dithiocarbamates include the alkali or alkaline earth metal salts wherein the anion is di-*n*-butyldithiocarbamate, di-*n*-propyldithiocarbamate, pentamethylenedithiocarbamate, or tetramethylene dithiocarbamate.

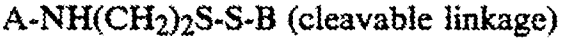
[0238] When the improvement is made by use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier to treat brain metastases of NSCLC or ovarian cancer, the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier can be, but is not limited to, an agent selected from the group consisting of:

(a) a chimeric peptide of the structure of Formula (D-III):



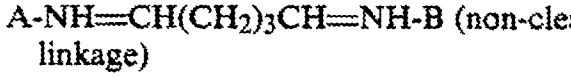
(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):



(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):



(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

(b) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

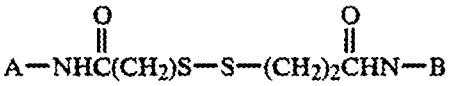
(c) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(d) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(e) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

[0239] Agents that improve penetration of the blood-brain barrier are disclosed in W.M. Pardridge, "The Blood-Brain Barrier: Bottleneck in Brain Drug Development," NeuroRx 2: 3-14 (2005), incorporated herein by this reference.

[0240] One class of these agents is disclosed in United States Patent No. 4,801,575 to Pardridge, incorporated herein by this reference, which discloses chimeric peptides for delivery of agents across the blood-brain barrier. These chimeric peptides include peptides of the general structure of Formula (D-IV):

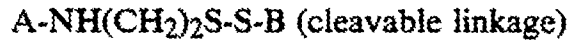


(D-IV)

wherein:

(i) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and

(ii) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin. In another alternative, the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-IV(a)):



(D-IV(a));

the bridge of Subformula (D-III(a)) is formed when cysteamine and EDAC are employed as the bridge reagents. In yet another alternative, the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-IV(b)):

(D-IV(b));

the bridge of Subformula (D-III(b)) is formed when glutaraldehyde is employed as the bridge reagent.

[0241] United States Patent No. 6,287,792 to Pardridge et al., incorporated herein by this reference, discloses methods and compositions for delivery of agents across the blood-brain barrier comprising either avidin or an avidin fusion protein bonded to a biotinylated agent to form an avidin-biotin-agent complex. The avidin fusion protein can include the amino acid sequences of proteins such as insulin or transferrin, an anti-receptor monoclonal antibody, a cationized protein, or a lectin.

[0242] United States Patent No. 6,372,250 to Pardridge, incorporated herein by this reference, discloses methods and compositions for delivery of agents across the blood-brain barrier employing liposomes. The liposomes are neutral liposomes. The surface of the neutral liposomes is pegylated. The polyethylene glycol strands are conjugated to transportable peptides or other targeting agents. Suitable targeting agents include insulin, transferrin, insulin-like growth factor, or leptin. Alternatively, the surface of the liposome could be conjugated with 2 different transportable peptides, one peptide targeting an endogenous BBB receptor and the other targeting an endogenous BCM (brain cell plasma membrane) peptide. The latter could be specific for particular

cells within the brain, such as neurons, glial cells, pericytes, smooth muscle cells, or microglia. Targeting peptides may be endogenous peptide ligands of the receptors, analogues of the endogenous ligand, or peptidomimetic MAbs that bind the same receptor of the endogenous ligand. Transferrin receptor-specific peptidomimetic monoclonal antibodies can be used as transportable peptides. Monoclonal antibodies to the human insulin receptor can be used as transportable peptides. The conjugation agents which are used to conjugate the blood-barrier targeting agents to the surface of the liposome can be any of the well-known polymeric conjugation agents such as sphingomyelin, polyethylene glycol (PEG) or other organic polymers, with PEG preferred. The liposomes preferably have diameters of less than 200 nanometers. Liposomes having diameters of between 50 and 150 nanometers are preferred. Especially preferred are liposomes or other nanocontainers having external diameters of about 80 nanometers. Suitable types of liposomes are made with neutral phospholipids such as 1-palmitoyl-2-oleoyl-*sn*-glycerol-3-phosphocholine (POPC), diphosphatidyl phosphocholine, distearoylphosphatidylethanolamine (DSPE), or cholesterol. The transportable peptide is linked to the liposome as follows: A transportable peptide such as insulin or an HIRMAb is thiolated and conjugated to a maleimide group on the tip of a small fraction of the PEG strands; or, surface carboxyl groups on a transportable peptide such as transferrin or a TfRMAb are conjugated to a hydrazide (Hz) moiety on the tip of the PEG strand with a carboxyl activator group such as N-methyl-N′-3(dimethylaminopropyl)carbodiimide hydrochloride (EDAC); a transportable peptide is thiolated and conjugated via a disulfide linker to the liposome that has been reacted with N-succinimidyl 3-(2-pyridylthio)propionate (SPDP); or a transportable peptide is conjugated to the surface of the liposome with avidin-biotin technology, e.g., the transportable peptide is mono-biotinylated and is bound to avidin or streptavidin (SA), which is attached to the surface of the PEG strand.

[0243] United States Patent No. 7,388,079 to Pardridge et al., incorporated herein by this reference, discloses the use of a humanized murine antibody that binds to the human insulin receptor; the humanized murine antibody can be linked to the agent to be delivered through an avidin-biotin linkage.

[0244] United States Patent No. 8,124,095 to Pardridge et al., incorporated herein by this reference, discloses monoclonal antibodies that are capable of binding to an endogenous blood-brain barrier receptor-mediated transport system and are thus capable of serving as a vector for transport of a therapeutic agent across the BBB. The monoclonal antibody can be, for example, an antibody specifically binding the human insulin receptor on the human BBB.

[0245] United States Patent Application Publication No. 2005/0085419 by Morrison et al., incorporated herein by this reference, discloses a fusion protein for delivery of a wide variety of agents to a cell via antibody-receptor-mediated endocytosis comprises a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative. Typically, the antigen is a protein. Typically, the protein antigen on the surface of the cell is a receptor such as a transferrin receptor-or an insulin receptor. The invention also includes an antibody construct incorporating the fusion protein that is either a heavy chain or a light chain together with a complementary light chain or heavy chain to form an intact antibody molecule. The therapeutic agent can be a non-protein molecule and can be linked covalently to biotin.

[0246] Another aspect of the present invention is a composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing a substituted hexitol derivative for the treatment of NSCLC or ovarian cancer comprising an alternative selected from the group consisting of:

(i) a therapeutically effective quantity of a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative, wherein the modified substituted hexitol derivative or the derivative, analog or prodrug of the substituted hexitol derivative or modified substituted hexitol derivative possesses increased therapeutic efficacy or

reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative;

(ii) a composition comprising:

(a) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative, or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative; and

(b) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, drug delivery system, agent to counteract myelosuppression, or agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative;

(iii) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is incorporated into a dosage form, wherein the substituted hexitol derivative, the modified substituted hexitol derivative or the derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative;

(iv) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is incorporated into a dosage kit and packaging, wherein the substituted hexitol derivative, the modified substituted hexitol derivative or the derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative incorporated into the dosage kit and packaging possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative; and

(v) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is subjected to a bulk drug product improvement, wherein substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative subjected to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative.

[0247] As detailed above, typically the unmodified substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol. Preferably, the unmodified substituted hexitol derivative is dianhydrogalactitol.

[0248] In one alternative, a composition according to the present invention possesses increased therapeutic efficacy or reduced side effects for treatment of both NSCLC and ovarian cancer. In another alternative, a composition according to the present invention possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC. In yet another alternative, a composition according to the present invention possesses increased therapeutic efficacy or reduced side effects for treatment of ovarian cancer.

[0249] In one alternative, the composition comprises a drug combination comprising:

(i) a substituted hexitol derivative; and

(ii) an additional therapeutic agent selected from the group consisting of:

(a) topoisomerase inhibitors;

(b) fraudulent nucleosides;

(c) fraudulent nucleotides;

(d) thymidylate synthetase inhibitors;

(e) signal transduction inhibitors;

(f) cisplatin, oxaliplatin, or another platinum analog;

(g) monofunctional alkylating agents;

(h) bifunctional alkylating agents;

(i) alkylating agents that damage DNA at a different place than does dianhydrogalactitol;

(j) anti-tubulin agents;

(k) antimetabolites;

(l) berberine;

(m) apigenin;

(n) amonafide;

(o) colchicine or analogs;

(p) genistein;

(q) etoposide;

(r) cytarabine;

(s) camptothecins;

(t) vinca alkaloids;

(u) 5-fluorouracil;

(v) curcumin;

(w) NF-κB inhibitors;

(x) rosmarinic acid;

(y) mitoguazone;

(z) tetrandrine;

(aa) temozolomide;

(ab) VEGF inhibitors;

(ac) cancer vaccines;

(ad) EGFR inhibitors;

(ae) tyrosine kinase inhibitors;

(af) poly (ADP-ribose) polymerase (PARP) inhibitors; and

(ag) ALK inhibitors.

[0250] These additional agents described above can be used in compositions including drug combinations together with the substituted hexitol derivative for treatment

of either NSCLC or ovarian cancer. The additional agent to be included is one that is either known to possess activity against the type of cancer being treated (NSCLC or ovarian cancer), is structurally related to a compound or a class of compounds known to possess activity against the type of cancer being treated, or is known to modulate a pathway for which modulation has been shown to be effective against the type of cancer being treated. As used herein, the term "modulation" can include either activation or inhibition of the pathway involved, but typically refers to inhibition of the pathway.

[0251] When compositions according to the present invention are intended for treatment of ovarian cancer, drug combinations included in the compositions can include a substituted hexitol derivative as described above together with an additional agent that possesses anti-neoplastic activity against ovarian tumors. Such additional agents include, but are not limited to, paclitaxel, docetaxel, cisplatin, carboplatin, topotecan, gemcitabine, bleomycin, etoposide, doxorubicin (which can be used in a pegylated liposomal form), tamoxifen, letrozole, olaparib, selumetinib, mTOR inhibitors, PI3 kinase inhibitors, and trichostatin A.

[0252] Additional agents that possess anti-neoplastic activity against NSCLC are known in the art. These additional agents can be included in compositions that include drug combinations according to the present invention in a therapeutically effective quantity together with a therapeutically effective quantity of a substituted hexitol derivative as described above. One or more than one of these additional agents can be included in the composition in the drug combination. These additional agents can be included in the composition together with one or more of the agents as described above for activity against NSCLC in drug combinations including a substituted hexitol derivative such as dianhydrogalactitol or diacetyldianhydrogalactitol. The agents are those collectively referred to herein as "Additional Secondary Agents with Activity Against NSCLC."

[0253] Additional agents that possess anti-neoplastic activity against ovarian cancer are known in the art. These additional agents can be included in compositions that include drug combinations according to the present invention in a therapeutically effective quantity together with a therapeutically effective quantity of a substituted hexitol derivative as described above. One or more than one of these additional agents

can be included in the composition in the drug combination. These additional agents can be included in the composition together with one or more of the agents as described above for activity against ovarian cancer in drug combinations including a substituted hexitol derivative such as dianhydrogalactitol or diacetyldianhydrogalactitol. The agents are those collectively referred to herein as "Additional Secondary Agents with Activity Against Ovarian Cancer."

[0254] In another alternative, the composition comprises:

(i) a substituted hexitol derivative; and

(ii) a therapeutic agent subject to chemosensitization selected from the group consisting of:

(a) topoisomerase inhibitors;

(b) fraudulent nucleosides;

(c) fraudulent nucleotides;

(d) thymidylate synthetase inhibitors;

(e) signal transduction inhibitors;

(f) cisplatin, oxaliplatin, or another platinum analog;

(g) alkylating agents;

(h) anti-tubulin agents;

(i) antimetabolites;

(j) berberine;

(k) apigenin;

(l) amonafide;

(m) colchicine or analogs;

(n) genistein;

(o) etoposide;

(p) cytarabine;

(q) camptothecins;

(r) vinca alkaloids;

(s) topoisomerase inhibitors;

(t) 5-fluorouracil;

(u) curcumin;

(v) NF-κB inhibitors;

(w) rosmarinic acid;

(x) mitoguazone;

(y) tetrandrine;

(z) a tyrosine kinase inhibitor;

(aa) an inhibitor of EGFR; and

(ab) an inhibitor of PARP;

wherein the substituted hexitol derivative acts as a chemosensitizer.

[0255] In still another alternative, the composition comprises:

(i) a substituted hexitol derivative; and

(ii) a therapeutic agent subject to chemopotentiation selected from the group consisting of:

(a) topoisomerase inhibitors;

(b) fraudulent nucleosides;

(c) fraudulent nucleotides;

(d) thymidylate synthetase inhibitors;

(e) signal transduction inhibitors;

(f) cisplatin, oxaliplatin, or another platinum analog;

(g) alkylating agents;

(h) anti-tubulin agents;

(i) antimetabolites;

(j) berberine;

(k) apigenin;

(l) amonafide;

(m) colchicine or analogs;

(n) genistein;

(o) etoposide;

(p) cytarabine;

(q) camptothecins;

(r) vinca alkaloids;

(s) 5-fluorouracil;

(t) curcumin;

(u) NF-κB inhibitors;

(v) rosmarinic acid;

(w) mitoguazone;

(x) tetrandrine;

(y) a tyrosine kinase inhibitor;

(z) an inhibitor of EGFR; and

(aa) an inhibitor of PARP;

wherein the substituted hexitol derivative acts as a chemopotentiator.

[0256] In yet another alternative, the substituted hexitol derivative is subjected to a bulk drug product improvement, wherein the bulk drug product improvement is selected from the group consisting of:

(a) salt formation;

(b) preparation as a homogeneous crystal structure;

(c) preparation as a pure isomer;

(d) increased purity;

(e) preparation with lower residual solvent content; and

(f) preparation with lower residual heavy metal content.

[0257] In still another alternative, the composition comprises a substituted hexitol derivative and a diluent, wherein the diluent is selected from the group consisting of:

(a) an emulsion;

(b) dimethylsulfoxide (DMSO);

(c) N-methylformamide (NMF)

(d) DMF;

(e) ethanol;

(f) benzyl alcohol;

(g) dextrose-containing water for injection;

(h) Cremophor;

(i) cyclodextrin; and

(j) PEG.

[0258] In still another alternative, the composition comprises a substituted hexitol derivative and a solvent system, wherein the solvent system is selected from the group consisting of:

(a) an emulsion;
(b) dimethylsulfoxide (DMSO);
(c) N-methylformamide (NMF)
(d) DMF;
(e) ethanol;
(f) benzyl alcohol;
(g) dextrose-containing water for injection;
(h) Cremophor;
(i) cyclodextrin; and
(j) PEG.

[0259] In yet another alternative, the composition comprises a substituted hexitol derivative and an excipient, wherein the excipient is selected from the group consisting of:

(a) mannitol;
(b) albumin;
(c) EDTA;
(d) sodium bisulfite;
(e) benzyl alcohol;
(f) a carbonate buffer; and
(g) a phosphate buffer.

[0260] In still another alternative, the substituted hexitol derivative is incorporated into a dosage form selected from the group consisting of:

(a) tablets;
(b) capsules;
(c) topical gels;
(d) topical creams;
(e) patches;
(f) suppositories; and

(g) lyophilized dosage fills.

[0261] In yet another alternative, the substituted hexitol derivative is incorporated into a dosage kit and packaging selected from the group consisting of amber vials to protect from light and stoppers with specialized coatings to improve shelf-life stability.

[0262] In still another alternative, the composition comprises a substituted hexitol derivative and a drug delivery system selected from the group consisting of:

(a) nanocrystals;

(b) bioerodible polymers;

(c) liposomes;

(d) slow release injectable gels; and

(e) microspheres.

[0263] In still another alternative, the substituted hexitol derivative is present in the composition in a drug conjugate form selected from the group consisting of:

(a) a polymer system;

(b) polylactides;

(c) polyglycolides;

(d) amino acids;

(e) peptides; and

(f) multivalent linkers.

[0264] In yet another alternative, the therapeutic agent is a modified substituted hexitol derivative and the modification is selected from the group consisting of:

(a) alteration of side chains to increase or decrease lipophilicity;

(b) addition of an additional chemical functionality to alter a property selected from the group consisting of reactivity, electron affinity, and binding capacity; and

(c) alteration of salt form.

[0265] In still another alternative, the substituted hexitol derivative is in the form of a prodrug system, wherein the prodrug system is selected from the group consisting of:

(a) the use of enzyme sensitive esters;

(b) the use of dimers;

(c) the use of Schiff bases;

(d) the use of pyridoxal complexes; and

(e) the use of caffeine complexes.

[0266] In yet another alternative, the composition comprises a substituted hexitol derivative and at least one additional therapeutic agent to form a multiple drug system, wherein the at least one additional therapeutic agent is selected from the group consisting of:

(a) an inhibitor of multi-drug resistance;

(b) a specific drug resistance inhibitor;

(c) a specific inhibitor of a selective enzyme;

(d) a signal transduction inhibitor;

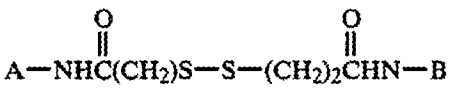
(e) an inhibitor of a repair enzyme; and

(f) a topoisomerase inhibitor with non-overlapping side effects.

[0267] In yet another alternative, the composition comprises a substituted hexitol derivative and an agent to counteract myelosuppression as described above. Typically, the agent to counteract myelosuppression is a dithiocarbamate.

[0268] In yet another alternative, the composition comprises a substituted hexitol derivative and an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier as described above. Typically, the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier is an agent selected from the group consisting of:

(a) a chimeric peptide of the structure of Formula (D-III):



(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric

peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):

$$A\text{-}NH(CH_2)_2S\text{-}S\text{-}B \text{ (cleavable linkage)}$$

(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):

$$A\text{-}NH{=}CH(CH_2)_3CH{=}NH\text{-}B \text{ (non-cleavable linkage)}$$

(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

(b) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(c) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(d) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(e) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

[0269] When a pharmaceutical composition according to the present invention includes a prodrug, prodrugs and active metabolites of a compound may be identified using routine techniques known in the art. See, e.g., Bertolini et al., J. Med. Chem., 40, 2011-2016 (1997); Shan et al., J. Pharm. Sci., 86 (7), 765-767; Bagshawe, Drug Dev. Res., 34, 220-230 (1995); Bodor, Advances in Drug Res., 13, 224-331 (1984); Bundgaard, Design of Prodrugs (Elsevier Press 1985); Larsen, Design and Application of Prodrugs, Drug Design and Development (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991); Dear et al., J. Chromatogr. B, 748, 281-293 (2000); Spraul et al., J. Pharmaceutical & Biomedical Analysis, 10, 601-605 (1992); and Prox et al., Xenobiol., 3, 103-112 (1992).

[0270] When the pharmacologically active compound in a pharmaceutical composition according to the present invention possesses a sufficiently acidic, a sufficiently basic, or both a sufficiently acidic and a sufficiently basic functional group, these group or groups can accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the pharmacologically active compound with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, β-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates. If the pharmacologically active compound has one or more basic functional groups, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid,

phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as *p*-toluenesulfonic acid or ethanesulfonic acid, or the like. If the pharmacologically active compound has one or more acidic functional groups, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0271] In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

[0272] The amount of a given pharmacologically active agent, such as a substituted hexitol derivative such as dianhydrogalactitol or an analog or derivative of dianhydrogalactitol as described above, that is included in a unit dose of a pharmaceutical composition according to the present invention will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the subject in need of treatment, but can nevertheless be routinely determined by one skilled in the art. Typically, such pharmaceutical compositions include a therapeutically effective quantity of the pharmacologically active agent and an inert pharmaceutically acceptable carrier or diluent. Typically, these compositions are prepared in unit dosage form appropriate for the chosen route of administration, such as oral administration or parenteral administration. A pharmacologically active agent as described above can be administered in conventional dosage form prepared by

combining a therapeutically effective amount of such a pharmacologically active agent as an active ingredient with appropriate pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. The pharmaceutical carrier employed may be either a solid or liquid. Exemplary of solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like.

[0273] A variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension.

[0274] To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of a pharmacologically active agent as described above is dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3 M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume. In an exemplary embodiment, a compound of Formula I is dissolved in DMSO and diluted with water. The composition may also be in the form of a solution of a salt form of the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

[0275] It will be appreciated that the actual dosages of the agents used in the compositions of this invention will vary according to the particular complex being used,

the particular composition formulated, the mode of administration and the particular site, host and disease and/or condition being treated. Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the subject. The selected dosage level depends upon a variety of pharmacokinetic factors including the activity of the particular therapeutic agent, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the severity of the condition, other health considerations affecting the subject, and the status of liver and kidney function of the subject. It also depends on the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular therapeutic agent employed, as well as the age, weight, condition, general health and prior medical history of the subject being treated, and like factors. Methods for determining optimal dosages are described in the art, e.g., Remington: *The Science and Practice of Pharmacy*, Mack Publishing Co., 20th ed., 2000. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests in view of the experimental data for an agent. For oral administration, an exemplary daily dose generally employed is from about 0.001 to about 3000 mg/kg of body weight, with courses of treatment repeated at appropriate intervals. In some embodiments, the daily dose is from about 1 to 3000 mg/kg of body weight. Other dosages are as described above.

[0276] Typical daily doses in a patient may be anywhere between about 500 mg to about 3000 mg, given once or twice daily, e.g., 3000 mg can be given twice daily for a total dose of 6000 mg. In one embodiment, the dose is between about 1000 to about 3000 mg. In another embodiment, the dose is between about 1500 to about 2800 mg. In other embodiments, the dose is between about 2000 to about 3000 mg. Typically, doses are from about 1 mg/m^2 to about 40 mg/m^2. Preferably, doses are from about 5 mg/m^2 to about 25 mg/m^2. Additional alternatives for dosages are as described above with respect to schedules of administration and dose modification. Dosages can be varied according to the therapeutic response.

[0277] Plasma concentrations in the subjects may be between about 100 μM to about 1000 μM. In some embodiments, the plasma concentration may be between about 200 μM to about 800 μM. In other embodiments, the concentration is about 300 μM to about 600 μM. In still other embodiments the plasma concentration may be between about 400 to about 800 μM. In another alternative, the plasma concentration can be between about 0.5 μM to about 20 μM, typically 1 μM to about 10 μM. Administration of prodrugs is typically dosed at weight levels, which are chemically equivalent to the weight levels of the fully active form.

[0278] The compositions of the invention may be manufactured using techniques generally known for preparing pharmaceutical compositions, e.g., by conventional techniques such as mixing, dissolving, granulating, dragee-making, levitating, emulsifying, encapsulating, entrapping or lyophilizing. Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers, which may be selected from excipients and auxiliaries that facilitate processing of the active compounds into preparations, which can be used pharmaceutically.

[0279] Proper formulation is dependent upon the route of administration chosen. For injection, the agents of the invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0280] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, solutions, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol,

or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0281] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

[0282] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0283] Pharmaceutical formulations for parenteral administration can include aqueous solutions or suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil or synthetic fatty acid esters, such as ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or modulators which increase the solubility or dispersibility of the composition to allow for the preparation of highly concentrated solutions, or can contain suspending or dispersing agents. Pharmaceutical preparations for oral use can be obtained by combining the pharmacologically active agent with solid excipients, optionally grinding a resulting

mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating modulators may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0284] Other ingredients such as stabilizers, for example, antioxidants such as sodium citrate, ascorbyl palmitate, propyl gallate, reducing agents, ascorbic acid, vitamin E, sodium bisulfite, butylated hydroxytoluene, BHA, acetylcysteine, monothioglycerol, phenyl-α-naphthylamine, or lecithin can be used. Also, chelators such as EDTA can be used. Other ingredients that are conventional in the area of pharmaceutical compositions and formulations, such as lubricants in tablets or pills, coloring agents, or flavoring agents, can be used. Also, conventional pharmaceutical excipients or carriers can be used. The pharmaceutical excipients can include, but are not necessarily limited to, calcium carbonate, calcium phosphate, various sugars or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Other pharmaceutical excipients are well known in the art. Exemplary pharmaceutically acceptable carriers include, but are not limited to, any and/or all of solvents, including aqueous and non-aqueous solvents, dispersion media, coatings, antibacterial and/or antifungal agents, isotonic and/or absorption delaying agents, and/or the like. The use of such media and/or agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional medium, carrier, or agent is incompatible with the active ingredient or ingredients, its use in a composition according to the present invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions, particularly as described above. For administration of any of the compounds used in the present invention, preparations should meet sterility, pyrogenicity, general safety, and purity standards as required by the FDA Office of Biologics Standards or by other regulatory organizations regulating drugs.

[0285] For administration intranasally or by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0286] The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0287] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents, which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0288] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0289] In addition to the formulations described above, the compounds may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0290] An exemplary pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

[0291] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days; in other alternatives, depending on the therapeutic agent and the formulation employed, release

may occur over hours, days, weeks, or months. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0292] The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0293] A pharmaceutical composition can be administered by a variety of methods known in the art. The routes and/or modes of administration vary depending upon the desired results. Depending on the route of administration, the pharmacologically active agent may be coated in a material to protect the targeting composition or other therapeutic agent from the action of acids and other compounds that may inactivate the agent. Conventional pharmaceutical practice can be employed to provide suitable formulations or compositions for the administration of such pharmaceutical compositions to subjects. Any appropriate route of administration can be employed, for example, but not limited to, intravenous, parenteral, intraperitoneal, intravenous, transcutaneous, subcutaneous, intramuscular, intraurethral, or oral administration. Depending on the severity of the malignancy or other disease, disorder, or condition to be treated, as well as other conditions affecting the subject to be treated, either systemic or localized delivery of the pharmaceutical composition can be used in the course of treatment. The pharmaceutical composition as described above can be administered together with additional therapeutic agents intended to treat a particular disease or condition, which may be the same disease or condition that the pharmaceutical composition is intended to treat, which may be a related disease or condition, or which even may be an unrelated disease or condition.

[0294] Pharmaceutical compositions according to the present invention can be prepared in accordance with methods well known and routinely practiced in the art. See, e.g., Remington: *The Science and Practice of Pharmacy*, Mack Publishing Co., 20th ed., 2000; and *Sustained and Controlled Release Drug Delivery Systems*, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978. Pharmaceutical compositions are preferably manufactured under GMP conditions. Formulations for parenteral

administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymers, lactide/glycolide copolymers, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for molecules of the invention include ethylene-vinyl acetate copolymer particles, osmotic pumps, and implantable infusion systems. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, e.g., polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or can be oily solutions for administration or gels.

[0295] Pharmaceutical compositions according to the present invention are usually administered to the subjects on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by therapeutic response or other parameters well known in the art. Alternatively, the pharmaceutical composition can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life in the subject of the pharmacologically active agent included in a pharmaceutical composition. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some subjects may continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the subject shows partial or complete amelioration of symptoms of disease. Thereafter, the subject can be administered a prophylactic regime.

[0296] For the purposes of the present application, treatment can be monitored by observing one or more of the improving symptoms associated with the disease, disorder, or condition being treated, or by observing one or more of the improving clinical parameters associated with the disease, disorder, or condition being treated. In the case of NSCLC, the clinical parameters can include, but are not limited to, reduction

in tumor burden, reduction in pain, improvement in lung function, improvement in Karnofsky Performance Score, and reduction in occurrence of tumor spread or metastasis. In the case of ovarian cancer, the similar clinical parameters can be applied, such as reduction in tumor burden, reduction in pain, reduction in abdominal symptoms, reduction in urinary tract symptons, improvement in Karnofsky Performance Score, and reduction in occurrence of tumor spread or metastasis. As used herein, the terms "treatment," "treating," or equivalent terminology are not intended to imply a permanent cure for the disease, disorder, or condition being treated. Compositions and methods according to the present invention are not limited to treatment of humans, but are applicable to treatment of socially or economically important animals, such as dogs, cats, horses, cows, sheep, goats, pigs, and other animal species of social or economic importance. Unless specifically stated, compositions and methods according to the present invention are not limited to the treatment of humans.

[0297] Sustained-release formulations or controlled-release formulations are well-known in the art. For example, the sustained-release or controlled-release formulation can be (1) an oral matrix sustained-release or controlled-release formulation; (2) an oral multilayered sustained-release or controlled-release tablet formulation; (3) an oral multiparticulate sustained-release or controlled-release formulation; (4) an oral osmotic sustained-release or controlled-release formulation; (5) an oral chewable sustained-release or controlled-release formulation; or (6) a dermal sustained-release or controlled-release patch formulation.

[0298] The pharmacokinetic principles of controlled drug delivery are described, for example, in B.M. Silber et al., "Pharmacokinetic/Pharmacodynamic Basis of Controlled Drug Delivery" in Controlled Drug Delivery: Fundamentals and Applications (J.R. Robinson & V.H.L. Lee, eds, 2d ed., Marcel Dekker, New York, 1987), ch. 5, pp. 213-251, incorporated herein by this reference.

[0299] One of ordinary skill in the art can readily prepare formulations for controlled release or sustained release comprising a pharmacologically active agent according to the present invention by modifying the formulations described above, such as according to principles disclosed in V.H.K. Li et al, "Influence of Drug Properties and Routes of Drug Administration on the Design of Sustained and Controlled Release

Systems" in Controlled Drug Delivery: Fundamentals and Applications (J.R. Robinson & V.H.L. Lee, eds, 2d ed., Marcel Dekker, New York, 1987), ch. 1, pp. 3-94, incorporated herein by this reference. This process of preparation typically takes into account physicochemical properties of the pharmacologically active agent, such as aqueous solubility, partition coefficient, molecular size, stability, and nonspecific binding to proteins and other biological macromolecules. This process of preparation also takes into account biological factors, such as absorption, distribution, metabolism, duration of action, the possible existence of side effects, and margin of safety, for the pharmacologically active agent. Accordingly, one of ordinary skill in the art could modify the formulations into a formulation having the desirable properties described above for a particular application.

[0300] United States Patent No. 6,573,292 by Nardella, United States Patent No. 6,921,722 by Nardella, United States Patent No. 7,314,886 to Chao et al., and United States Patent No. 7,446,122 by Chao et al., which disclose methods of use of various pharmacologically active agents and pharmaceutical compositions in treating a number of diseases and conditions, including cancer, and methods of determining the therapeutic effectiveness of such pharmacologically active agents and pharmaceutical compositions, are all incorporated herein by this reference.

[0301] In view of the results reported in the Examples below, another aspect of the present invention is a method of treating NSCLC comprising the step of administering a therapeutically effective quantity of a substituted hexitol derivative such as dianhydrogalactitol to a patient suffering from the malignancy.

[0302] Typically, when the substituted hexitol derivative is dianhydrogalactitol, the therapeutically effective quantity of dianhydrogalactitol is from about 1 mg/m^2 to about 40 mg/m^2. Preferably, the therapeutically effective quantity of dianhydrogalactitol is from about 5 mg/m^2 to about 25 mg/m^2. Therapeutically active quantities of substituted hexitol derivatives other than dianhydrogalactitol can be determined by one of ordinary skill in the art by using the molecular weight of the particular substituted hexitol derivative and the activity of the particular substituted hexitol derivative, such as the *in vitro* activity of the substituted hexitol derivative against a standard cell line.

Other suitable dosages are described above with respect to dose modification and schedule of administration and also in the Examples.

[0303] Typically, the substituted hexitol derivative such as dianhydrogalactitol is administered by a route selected from the group consisting of intravenous and oral. Preferably, the substituted hexitol derivative such as dianhydrogalactitol is administered intravenously.

[0304] The method can further comprise the step of administering a therapeutically effective dose of ionizing radiation. The method can further comprise the step of administering a therapeutically effective dose of an additional chemotherapeutic agent selected from the group consisting of cisplatin, carboplatin, oxaliplatin, bevacizumab, paclitaxel, Abraxane (paclitaxel bound to albumin as a delivery vehicle), docetaxel, etoposide, gemcitabine, vinorelbine tartrate, and pemetrexed. Suitable methods for administration of these agents and suitable dosages are well known in the art.

[0305] Typically, the substituted hexitol derivative such as dianhydrogalactitol substantially suppresses the growth of cancer stem cells (CSCs). Typically, the suppression of the growth of cancer stem cells is at least 50%. Preferably, the suppression of the growth of cancer stem cells is at least 99%.

[0306] Typically, the substituted hexitol derivative such as dianhydrogalactitol is effective in suppressing the growth of cancer cells possessing O^6-methylguanine-DNA methyltransferase (MGMT)-driven drug resistance. Typically, the substituted hexitol derivative such as dianhydrogalactitol is also effective in suppressing the growth of cancer cells resistant to temozolomide.

[0307] The method can further comprise the administration of a therapeutically effective quantity of a tyrosine kinase inhibitor as described above.

[0308] The method can further comprise the administration of a therapeutically effective quantity of an epidermal growth factor receptor (EGFR) inhibitor as described above. The EGFR inhibitor can affect either wild-type binding sites or mutated binding sites, including EGFR Variant III, as described above.

[0309] Additionally, to treat brain metastases of NSCLC, the method can further comprise administering to the patient a therapeutically effective quantity of an agent that

increases the ability of the substituted hexitol to pass through the blood-brain barrier. Alternatively, the method can further comprise administering to the patient a therapeutically effective quantity of an agent to counteract myelosuppression.

[0310] In view of the results reported in the Examples below, another aspect of the present invention is a method of treating ovarian cancer comprising the step of administering a therapeutically effective quantity of a substituted hexitol derivative such as dianhydrogalactitol to a patient suffering from the malignancy.

[0311] Typically, when the substituted hexitol derivative is dianhydrogalactitol, the therapeutically effective quantity of dianhydrogalactitol is from about 1 mg/m^2 to about 40 mg/m^2. Preferably, the therapeutically effective quantity of dianhydrogalactitol is from about 5 mg/m^2 to about 25 mg/m^2. Therapeutically active quantities of substituted hexitol derivatives other than dianhydrogalactitol can be determined by one of ordinary skill in the art by using the molecular weight of the particular substituted hexitol derivative and the activity of the particular substituted hexitol derivative, such as the *in vitro* activity of the substituted hexitol derivative against a standard cell line. Other suitable dosages are described above with respect to dose modification and schedule of administration and also in the Examples.

[0312] Typically, the substituted hexitol derivative such as dianhydrogalactitol is administered by a route selected from the group consisting of intravenous and oral. Preferably, the substituted hexitol derivative such as dianhydrogalactitol is administered intravenously.

[0313] The method can further comprise the step of administering a therapeutically effective dose of ionizing radiation. The method can further comprise the step of administering a therapeutically effective dose of an additional chemotherapeutic agent selected from the group consisting of cisplatin, carboplatin, oxaliplatin, bevacizumab, paclitaxel, Abraxane (paclitaxel bound to albumin as a delivery vehicle), docetaxel, etoposide, gemcitabine, vinorelbine tartrate, and pemetrexed. Suitable methods for administration of these agents and suitable dosages are well known in the art. When ovarian cancer is treated, additional therapeutic agents that are or may be effective against ovarian cancer can also be administered; these agents are described in further detail below.

[0314] Typically, the substituted hexitol derivative such as dianhydrogalactitol substantially suppresses the growth of cancer stem cells (CSCs). Typically, the suppression of the growth of cancer stem cells is at least 50%. Preferably, the suppression of the growth of cancer stem cells is at least 99%.

[0315] Typically, the substituted hexitol derivative such as dianhydrogalactitol is effective in suppressing the growth of cancer cells possessing O^6-methylguanine-DNA methyltransferase (MGMT)-driven drug resistance. Typically, the substituted hexitol derivative such as dianhydrogalactitol is also effective in suppressing the growth of cancer cells resistant to temozolomide.

[0316] The method can further comprise the administration of a therapeutically effective quantity of a tyrosine kinase inhibitor as described above.

[0317] Typically, the effect of administration of dianhydrogalactitol and a platinum-containing agent selected from the group consisting of cisplatin and oxaliplatin is at least additive. In some cases, the effect of administration of both of these agents is super-additive.

[0318] As stated above and as provided below in the Examples, substituted hexitol derivatives such as dianhydrogalactitol can also be used to treat ovarian cancer.

[0319] The risk of ovarian cancer increases with the frequency and duration of ovulation. Other risk factors include post-menopausal hormone therapy, fertility medication, and obesity. About 10% of the cases are related to increased genetic risk; women with the genetic mutations *BRCA1* or *BRCA2* can have up to a 50% risk of developing ovarian cancer. Such mutations occur more frequently in individuals with certain particular ethnic backgrounds, such as Ashkenazi Jews (Jews who can trace their ancestry to regions such as Germany, Austria, Poland, Hungary, Romania, the Czech Republic, Slovakia, Ukraine, Belarus, Lithuania, Latvia, or Russia), although they can occur in individuals with any ethnic background.

[0320] The most common type of ovarian cancer, comprising more than 95% of cases, is ovarian carcinoma. There are five main subtypes of ovarian carcinoma, of which high-grade serous is most common. These tumors are believed to start in the cells covering the ovaries, though some may form at the Fallopian tubes. Less common types include germ cell tumors and sex cord stromal tumors. As symptoms of ovarian

cancer are frequently absent in early stages of the disease and, if present, are typically generic and not clearly attributable to ovarian cancer, confirmation requires a biopsy.

[0321] Current treatment modalities include some combination of surgery, radiotherapy, and chemotherapy. However, the overall five-year survival rate in the United States is only about 45%. Current chemotherapies used for ovarian cancer include paclitaxel, docetaxel, cisplatin, carboplatin, gemcitabine, topotecan, etoposide, and doxorubicin. Other platinum-containing drugs, such as oxaliplatin, satraplatin, picoplatin, nedaplatin, triplatin, and lipoplatin can also be used. Olaparib, a PARP inhibitor, has been recently developed for ovarian cancer chemotherapy. However, in a substantial fraction of the cases, the tumor develops resistance to platinum-containing drugs. In cases of recurrent malignancy, carboplatin can also be combined with gemcitabine or paclitaxel. Tamoxifen or letrozole can be used, but are generally ineffective. Still other drugs such as selumetinib, mTOR inhibitors, and PI3 kinase inhibitors have been proposed. Additionally, histone deacetylase (HDAC) inhibitors such as trichostatin A have also been proposed as anti-ovarian cancer agents.

[0322] For most ovarian cancers, monitoring is performed by assessing the level of an antigen known as CA-125, also known as mucin 16, encoded by *MUC16*. This antigen is a protein antigen that is a membrane associated mucin that contains a single transmembrane domain.

[0323] Accordingly, one aspect of the present invention is a method of treating ovarian cancer comprising the step of administering a therapeutically effective quantity of a substituted hexitol derivative to a patient suffering from ovarian cancer. Suitable substituted hexitol derivatives are as described above; a particularly preferred substituted hexitol derivative is dianhydrogalactitol. Typically, the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 1 mg/m^2 to about 40 mg/m^2. Preferably, the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 5 mg/m^2 to about 25 mg/m^2. Typically, the the dianhydrogalactitol is administered by a route selected from the group consisting of intravenous and oral.

[0324] In one alternative, the ovarian cancer is a cisplatin-resistant wild-type p53 cancer.

[0325] In methods according to the present invention, a substituted hexitol as described above can be employed in a therapeutically effective quantity together with a therapeutically effective quantity of one or more antineoplastic agents for the treatment of ovarian cancer. Typically, as described above, the substituted hexitol is dianhydrogalactitol. Suitable agents that possess anti-neoplastic activity against ovarian tumors include, but are not limited to: paclitaxel, docetaxel, cisplatin, carboplatin, topotecan, gemcitabine, bleomycin, etoposide, doxorubicin (which can be used in a pegylated liposomal form), tamoxifen, letrozole, olaparib, selumetinib, mTOR inhibitors, PI3 kinase inhibitors, and trichostatin A.

[0326] Typically, the substituted hexitol derivative suppresses the growth of cancer stem cells. Typically, the substituted hexitol derivative suppresses the growth of cancer cells possessing O^6-methylguanine-DNA methyltransferase (MGMT)-driven drug resistance.

[0327] In another alternative, the method further comprises the step of administering a therapeutically effective quantity of a platinum-containing chemotherapeutic agent and wherein the platinum-containing chemotherapeutic agent is selected from the group consisting of cisplatin, carboplatin, iproplatin, oxaliplatin, tetraplatin, satraplatin, picoplatin, nedaplatin, and triplatin.

[0328] Additional agents that possess anti-neoplastic activity against ovarian tumors are known in the art. United States Patent No. 8,981,131 to Bhedi et al., discloses the use of tricyclic compounds such as (5aR,9bS)-3a-hydroxy-5a,9-dimethyl-3-((4-methylpiperazin-1-yl)methyl)-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-b]furan-2(9bH)-one hydrochloride; ethyl 4-(((5aR,9bS)-3a-hydroxy-5a,9-dimethyl-2-oxo-2,3,3a,4,5,5a,6,7,8,9b-decahydronaphtha[1,2-b]furan-3-yl)methyl)piperazine-1-carboxylate hydrochloride; (5aR,9bS)-3a-hydroxy-5a,9-dimethyl-3-((4-o-tolylpiperazin-1-yl)methyl)-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-b]furan-2(9bH)-one hydrochloride; or (5aR,9bR)-3a-hydroxy-3-((((5aR,9bS)-3a-hydroxy-5a,9-dimethyl-2-oxo-2,3,3a,4,5,5a,6,7,8,9b-decahydronaphtho[1,2-b]furan-3-yl)methylamino)methyl)-5a,9-dimethyl-3,3a,4,5,5a,6,7,8-octahydronaphtho[1,2-b]furan-2(9bH)-one hydrochloride).

United States Patent No. 8,981,094 to Bongartz et al. discloses the use of piperidine/piperazine derivatives that are DGAT inhibitors, particularly DGAT1 inhibitors. United States Patent No. 8,981,085 to Le Huerou et al. discloses the use of pyrrolopyrimidine CHK1 or CHK2 inhibitors. United States Patent No. 8,981,084 to Balogu et al. discloses the use of oxadiazole HDAC inhibitors. United States Patent No. 8,980,955 to Turchi et al. discloses the use of inhibitors of Replication Protein A that are haloester isoborneol derivatives. United States Patent No. 8,980,934 to Pauls et al. discloses the use of indazole inhibitors of TTK protein kinase. United States Patent No. 8,980,933 to Schobert et al. discloses the use of combretastatin analogs. United States Patent No. 8,980,909 to Chen et al. discloses the use of HDAC inhibiting derivatives of camptothecin. United States Patent No. 8,980,902 to Brown et al. discloses the use of piperazinylbenzamide PARP inhibitors. United States Patent No. 8,980,879 to Liu et al. discloses the use of BET bromodomain inhibitors including 5-(cyclopropylmethyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; 5-(4-fluorophenyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; 5-(2,4-difluorophenyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; 5-(cyclopropanecarbonyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; 5-(4-fluorophenyl)-4-(2-methoxyethyl)-11-methyl-8-((methylsulfonyl)methyl)-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-1-one; methyl 3-(5-(4-fluorophenyl)-11-methyl-8-((methylsulfonyl)methyl)-1-oxo-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-4-yl)propanoate; N-(5-(4-fluorophenyl)-11-methyl-1-oxo-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-8-yl)ethanesulfonamide; 8-fluoro-5-(4-fluorophenyl)-11-methyl-2,4,5,11-tetrahydro-1H-2,5,6,11-tetraazadibenzo[cd,h]azulen-1-one; N-(5-(4-fluorophenyl)-11-methyl-1-oxo-2,4,5,11-tetrahydro-1H-2,5,6,11-tetraazadibenzo[cd,h]azulen-8-yl)-2-(1-methyl-1H-pyrazol-4-yl)acetamide; 8-amino-5-(4-fluorophenyl)-11-methyl-2,4,5,11-tetrahydro-1H-2,5,11-triaza- dibenzo[cd,h]azulen-1-one; N-(5-(4-fluorophenyl)-11-methyl-1-oxo-2,4,5,11-tetrahydro-1H-2,5,11-triazadibenzo[cd,h]azulen-8-yl)benzenesulfonamide; N-(4-(N-(5-(4-fluorophenyl)-11-methyl-1-oxo-2,4,5,11-tetrahydro-1H-2,5,11-

triazadibenzo[cd,h]azulen-8-yl)sulfamoyl)phenyl)acetamide. United States Patent No. 8,980,875 to Mailliet et al. discloses the use of platinum N-heterocyclic carbene derivatives. United States Patent No. 8,980,850 to Smith discloses the use of NEDD8-activating enzyme inhibitors such as ((1S,2S,4R)-4-(4-((1S)-2,3-dihydro-1H-inden-1-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxycyclopentyl)methyl sulfamate or {(1S,2S,4R)-4-[(6-{[(1R,2S)-5-chloro-2-methoxy-2,3-dihydro-1H-inden-1-yl]amino}pyrimidin-4-yl)oxy]-2-hydroxycyclopentyl}methyl sulfamate. United States Patent No. 8,980,838 to Wang et al. discloses the use of cyclic peptidomimetic inhibitors of the WDR5/MLL1 interaction. United States Patent No. 8,980,268 to Lowy et al. discloses the use of anti-Ang-2 antibodies. United States Patent No. 8,980,257 to Kaneda et al. discloses the use of anti-TGFα antibodies. United States Patent No. 8,975,398 to Hansen et al. discloses the use of NAMPT inhibitors such as N-{4-[1-(2-methylpropanoyl)piperidin-4-yl]phenyl})-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(2-chlorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-[4-({1-[(2S)-2-methylbutanoyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(1,3-thiazol-2-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(tetrahydro-2H-pyran-4-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; N-[4-({1-[difluoro(phenyl)acetyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-[4-({1-[(4,4-difluorocyclohexyl)carbonyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(2-methyl-2-phenylpropanoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(1,3-thiazol-4-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; N-[4-({1-[(5-methylthiophen-2-yl)carbonyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-{4-[(1-{[4-(trifluoromethyl)phenyl]acetyl}piperidin-4-yl)oxy]phenyl}azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-[4-({1-[3-(trifluoromethyl)benzoyl]piperidin-4-yl}oxy)phenyl]azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(thiophen-3-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-[4-({1-[3-(trifluoromethoxy)benzoyl]piperidin-4-

yl}oxy)phenyl]azetidine-3-carboxamide; N-(4-{[1-(3-methylbutanoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; 1-(pyridazin-3-yl)-N-(4-{[1-(tetrahydrofuran-3-ylcarbonyl)piperidin-4-yl]oxy}phenyl)azetidine-3-carboxamide; N-[4-({1-[(3-fluorophenyl)acetyl]piperidin-4-yl}oxy)phenyl]-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(2-fluorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(2,4-difluorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; N-(4-{[1-(4-fluorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide; and N-(4-{[1-(3-fluorobenzoyl)piperidin-4-yl]oxy}phenyl)-1-(pyridazin-3-yl)azetidine-3-carboxamide. United States Patent No. 8,975,376 to Blein et al. discloses the use of anti-α_2-integrin antibodies. United States Patent No. 8,975,287 to Karp et al. discloses the use of 1,2,4-oxadiazole benzoic acid compounds. United States Patent No. 8,975,267 to Caldarelli et al. discloses the use of tricylic pyrrole derivatives such as N-(2,6-diethylphenyl)-9-(methoxymethyl)-2-{[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}-8-methyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, 2-[(4-bromo-2-methoxyphenyl)amino]-N-(2,6-diethylphenyl)-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, N-(2,6-diethylphenyl)-2-({2-methoxy-4-[4-(pyrrolidin-1-yl)piperidin-1-yl]phenyl}amino)-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, N-(2,6-diethylphenyl)-2-({4-[4-(dimethylamino)piperidin-1-yl]-2-methoxyphenyl}amino)-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, N-(2,6-diethylphenyl)-2-{[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, N-(2,6-diethylphenyl)-2-({4-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methoxyphenyl}amino)-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, 2-{[2-methoxy-4-(4-methylpiperazin-1-yl)phenyl]amino}-8,9-dimethyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide, and 2-[(4-bromo-2-methoxyphenyl)amino]-N-(2,6-diethylphenyl)-9-methyl-6,9-dihydro-5H-pyrrolo[3,2-h]quinazoline-7-carboxamide. United States Patent No. 8,974,781 to Bauer et al. discloses the use of anti-P-cadherin antibodies. United States Patent No. 8,969,587 to Abraham et al. discloses the use of BRAF kinase inhibitors, such as 1-(3-(6,7-dimethoxyquinazolin-4-yloxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea. United States Patent No.

8,969,401 to Maier et al. discloses the use of sulfonylpyrroles as HDAC inhibitors. United States Patent No. 8,969,396 to Du et al. discloses the use of BRAF inhibitors including Hsp90 inhibitors such as 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole. United States Patent No. 8,969,395 to Ribeiro Salvador et al. discloses the use of triterpenoid derivatives. United States Patent No. 8,969,381 to Wilson et al. discloses the use of chemokine CXCR4 modulators such as N^1-(((S)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine; N^1-(((R)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine; N^1-(((S)-4-benzylpiperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine; and N^1-(((R)-4-benzylpiperazin-2-yl)methyl)-N^1-((S)-5,6,7,8-tetrahydroquinolin-8-yl)butane-1,4-diamine. United States Patent No. 8,969,379 to Furitsu et al. discloses the use of 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide. United States Patent No. 8,969,375 to Lai et al. discloses the use of CDK9 kinase inhibitors such as 4-[1-(3-fluorobenzyl)-2,3-dihydro-1H-indol-6-yl]-2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine; 1-(3-fluorobenzyl)-6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-benzimidazole; 1-benzyl-6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-indole-3-carbonitrile; 1-(3-fluorobenzyl)-6-{2-[1-(methylsulfonyl)piperidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-1H-benzimidazole; 6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole; 6-{2-[1-(methylsulfonyl)piperidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazole; 5-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-imidazo[4,5-b]pyridine; 1-(3-fluorobenzyl)-6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-indole-3-carbonitrile; 4-[5-fluoro-1-(3-fluorobenzyl)-1H-indol-6-yl]-2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine; 6-{2-[1-(2,3-dihydroxypropyl)piperidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-1-(3-fluorobenzyl)-1H-indole-3-carbonitrile; 1-(3-fluorobenzyl)-6-{2-[1-(methylsulfonyl)piperidin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-1H-indole-3-carbonitrile; and 1-[(5-fluoropyridin-3-yl)methyl]-6-[2-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-1H-benzimidazole. United States Patent No. 8,969,366 to Marchionni et al. discloses the use of substituted pyrimidinylpyrrolopyridinone derivatives. United States Patent No. 8,969,360 to Charrier et al. discloses the use of inhibitors of ATR

kinase. United States Patent No. 8,969,335 to Hoelzemann et al. discloses the use of inhibitors of IKKε and TBK1 including benzonitrile derivatives. United States Patent No. 8,969,313 to Yu discloses the use of DACT protein activators. United States Patent No. 8,962,855 to Chen et al. discloses the use of nitrogen mustard derivatives. United States Patent No. 8,962,679 to Wang et al. discloses the use of daidzein derivatives including alkoxychromenon-4-ones. United States Patent No. 8,962,663 to Mahadevan et al. discloses the use of pleckstrin homology domain inhibitors. United States Patent No. 8,962,642 to Mortimore et al. discloses the use of 5-cyano-4-(pyrrolo [2,3-b] pyridine-3-yl)pyrimidine derivatives. United States Patent No. 8,962,637 to McAllister et al. discloses the use of substituted aromatic bicyclic compounds as c-SRC/JAK inhibitors. United States Patent No. 8,962,630 to Brain et al. discloses the use of pyrrolopyrimidine compounds including 7-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide as CDK protein kinase inhibitors. United States Patent No. 8,962,620 to Kuntz et al. discloses the use of substituted 6,5-fused bicyclic aryl compounds. United States Patent No. 8,962,619 to Ashwell et al. discloses the use of substituted imidazopyridinyl-aminopyridine compounds. United States Patent No. 8,962,611 to Christopher et al. discloses the use of substituted imidazopyridines as HDM2 inhibitors. United States Patent No. 8,962,608 to Brubaker et al. discloses the use of cycloalkylnitrile pyrazole carboxamides as janus kinase inhibitors. United States Patent No. 8,961,966 to Schoeberl et al. discloses the use of anti-ERBB3 antibodies. United States Patent No. 8,957,109 to Heaton et al. discloses the use of chroman derivatives. United States Patent No. 8,957,103 to Dannhardt et al. discloses the use of conjugated 3-(indolyl)- and 3-(azaindolyl)-4-arylmaleimide compounds. United States Patent No. 8,957,102 to Kim et al. discloses the use of c-Met inhibitors including 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid [3-fluoro-4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)-phenyl]-amide; 2-(4-fluoro-phenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid [3-fluoro-4-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)-phenyl]-am- ide; 2-(4-fluoro-phenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid [3-fluoro-4-(3-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)-phenyl]-amide; N-(3-fluoro-4-(2-(thiophen-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)- -2-(4-fluorophenyl)-1,5-

dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide; and N-(3-fluoro-4-(2-(thiophen-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxamide. United States Patent No. 8,957,078 to Brenchley et al. discloses the use of pyrazolopyrimidines as ATR kinase inhibitors. United States Patent No. 8,957,068 to Caferro et al. discloses the use of 3-pyrimidin-4-yl-oxazolidin-2-ones as inhibitors of mutant IDH. United States Patent No. 8,957,056 to Danishefsky et al. discloses the use of migrastatin analogs. United States Patent No. 8,956,613 to Wu et al. discloses the use of gemcitabine prodrugs. United States Patent No. 8,952,163 to Blackburn discloses the use of substituted hydroxamic acids as HDAC6 inhibitors. United States Patent No. 8,952,161 to Beaton et al. discloses the use of gonadotrophin-releasing hormone receptor antagonists. United States Patent No. 8,952,157 to Ding et al. discloses the use of inhibitors of anti-apoptotic Bcl-2 proteins such as 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,3-difluorophenoxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 2-(4-amino-3-chlorophenoxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2,5-dichlorophenoxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; N-(4-((4-aminotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrophenylsulfonyl)-2-(3-chlorophenoxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(3-fluorophenoxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 2-(2-chlorophenoxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 2-(2-chloro-4-fluorophenoxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2-fluorophenoxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(2-

fluorophenoxy)-N-({4-[(2-morpholin-4-ylethyl)amino]-3-nitrophenyl}sulfonyl)benzamide; and 2-(3-chlorophenoxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide. United States Patent No. 8,952,054 to Kufe et al. discloses the use of small molecule inhibitors of MUC1 oligomerization such as flavone derivatives. United States Patent No. 8,952,043 to Blaquiere et al. discloses the use of benzoxepin PI3K inhibitors. United States Patent No. 8,951,987 to Hamilton et al. discloses the use of tetrahydrouridine derivatives. United States Patent No. 8,951,536 to Combs et al. discloses the use of N-hydroxyamidino heterocycles as modulators of indoleamine 2,3-dioxygenase. United States Patent No. 8,946,445 to Wang discloses the use of heterocyclic apoptosis inhibitors such as (Z)-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-4H-thieno[3,2-b]pyrrole (Z)-2-chloro-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-4H-thieno[3,2-b]pyrrole; (Z)-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-2-methyl-4H-thieno[3,2-b]pyrrole; (Z)-2-bromo-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-4H-thieno[3,2-b]pyrrole; (Z)-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-6H-thieno[2,3-b]pyrrole; and (Z)-5-(2-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-2-methyl-6H-thieno[2,3-b]pyrrole. United States Patent No. 8,946,413 to Hughes et al. discloses the use of 3-aminocyclopentanecarboxamides as chemokine receptor antagonists. United States Patent No. 8,946,409 to Becker et al. discloses the use of polycyclic β-lactam derivatives. United States Patent No. 8,946,289 to Hong et al. discloses the use of manassatin compounds that block the HIF pathway. United States Patent No. 8,946,278 to Seefeld et al. discloses the use of heterocyclic carboxamides as AkT inhibitors, such as N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-

(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; and N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide. United States Patent No. 8,946,205 to Curd et al. discloses the use of hypoxia activated prodrugs, including N,N′-bis(2-bromoethyl)phosphorodamidic acid (1-methyl-2-nitro-1H-imidazol-5-yl)methyl ester. United States Patent No. 8,946,239 to Gangjee discloses the use of substituted pyrrolo-, furano-, and cyclopentylpyrimidine bicyclic compounds. United States Patent No. 8,946,235 to Butterworth et al. discloses the use of 2-(2,4,5-substituted-anilino)pyrimidine compounds. United States Patent No. 8,946,224 to Craighead et al. discloses the use of substituted [1,2,4]triazolo[4,3-a]pyrazines. United States Patent No. 8,946,216 to Deng et al. discloses the use of indazole derivatives as ERK inhibitors, including N-[3-[6-(1-methylethoxy)-3-pyridinyl]-1H-indazol-5-yl]-4-(phenylmethyl)-2-morpholinecarboxamide; N-[3-[6-(1-methylethoxy)-3-pyridinyl]-1H-indazol-5-yl]-2-morpholinecarboxamide; N-[3-(4-pyridinyl)-1H-indazol-5-yl]-4-(4-thiazolylmethyl)-2-morpholinecarboxamide; N-[3-(4-pyridinyl)-1H-indazol-5-yl]-4-(3-thienylmethyl)-2-morpholinecarboxamide; 4-[(2-fluorophenyl)methyl]-N-[3-(4-pyridinyl)-1h-indazol-5-yl]-2-morpholinecarboxamide; N-[3-(4-pyridinyl)-1H-indazol-5-yl]-4-(2-pyridinylmethyl)-2-morpholinecarboxamide; N-[3-(4-pyridinyl)-1H-indazol-5-yl]-4-(2-pyridinylmethyl)-2-morpholinecarboxamide; and 4-[(2-bromophenyl)methyl]-N-[3-(4-pyridinyl)-1H-indazol-5-yl]-2-morpholinecarboxamide. United States Patent No. 8,940,936 to Lee et al. discloses the use of aryloxy phenoxy acrylic compounds. United States Patent No. 8,940,760 to Page et al. discloses the use of pyrazolopyridine derivatives as NADPH oxidase inhibitors. United States Patent No. 8,940,756 to Flynn et al. discloses the use of dihydronaphthyridines as c-Kit inhibitors. United States

Patent No. 8,940,737 to Wang et al. discloses the use of apoptosis-inducing agents, such as 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-benzyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-(pyridin-4-ylmethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-(4-hydroxybenzyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-- [1-(1-phenylethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-{4-[2-(dimethylamino)ethoxy]benzyl}-1H-pyrazol-4-yl)pyridine-2-carboxylic acid; 3-(1-benzyl-1H-pyrazol-4-yl)-6-{8-[(5,6-difluoro-1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-{1-[2-(4-fluorophenyl)ethyl]-1H-pyrazol-4-yl}pyridine-2-carboxylic acid; 6-[8-(1,3-benzothiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl]-3-[1-(3-chlorobenzyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid; and 3-(1-benzyl-1H-pyrazol-4-yl)-6-{8-[(6-fluoro-1,3-benzothiazol-2-yl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}pyridine-2-carboxylic acid. United States Patent No. 8,940,733 to Howard et al. discloses the use of unsymmetrical pyrrolobenzodiazepine dimers. United States Patent No. 8,940,726 to Duncan et al. discloses the use of PRMT5 inhibitors. United States Patent No. 8,937,193 to Pellecchia et al. discloses the use of apogossypolone derivatives. United States Patent No. 8,937,094 to Burlison et al. discloses the use of Hsp90 modulators, including 5-(4-ethoxy-2-hydroxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-methoxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-propoxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-isopropoxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2,4-dimethoxyphenyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-isopropylphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(2-hydroxy-4-methylphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-

carboxamide; 5-(4-hydroxy-3-isopropylphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide; 5-(3-tert-butyl-4-hydroxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide; and 5-(4-hydroxy-3-propylphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-carboxamide. United States Patent No. 8,937,068 to Seipelt et al. discloses the use of pyridopyrazine compounds. United States Patent No. 8,933,212 to Fayard et al. discloses the use of protease nexin 1 inhibitors to reduce metastasis. United States Patent No. 8,933,116 to Wu et al. discloses the use of γ-secretase inhibitors. United States Patent No. 8,933,103 to Ohki et al. discloses the use of Axl inhibitors that are pyridone derivatives including N-{4-[2-amino-5-(3,4-dimethoxyphenyl)pyridin-3-yl]phenyl}-5-(4-fluorophenyl)-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydropyridine-3-carboxamide hydrochloride. United States Patent No. 8,933,084 to Andrews et al. discloses the use of macrocyclic compounds as Trk inhibitors such as (6R)-9-fluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione. United States Patent No. 8,933,080 to Singh et al. discloses the use of bridged bicyclic heteroaryl substituted triazoles as Axl inhibitors. United States Patent No. 8,933,053 to McGuigan et al. discloses the use of phosphoramidate derivatives of 5-fluoro-2′-deoxyuridine. United States Patent No. 8,927,718 to Sasaki et al. discloses the use of fused heterocyclic ring derivatives as Smo inhibitors, including 3,6-diethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide; 3-ethenyl-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide; and 6-Ethyl-3-(ethylamino)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide. United States Patent No. 8,927,717 to Huang et al. discloses the use of thiochromeno[2,3-c]quinolin-12-one derivatives including 3-((4-chlorophenyl)thio)-2-hydroxyquinoline-4-carboxylic acid, 6,9-dichloro-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-hydroxy-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-methoxy-12H-thiochromeno[2,3-c]quinolin-12-one 10-chloro-6-dimethylamino-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-(piperazin-1-yl)-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-(4-methylpiperazin-1-yl)-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-(4-

ethylpiperazin-1-yl)-12H-thiochromeno[2,3-c]quinolin-12-one, 10-chloro-6-(4-(2-hydroxyethyl)piperazin-1-yl)-12H-thiochromeno[2,3-c]quinolin-12-one, and 6-(4-benzylpiperazin-1-yl)-10-chloro-12H-thiochromeno[2,3-c]quinolin-12-one. United States Patent No. 8,927,711 to Abraham et al. discloses the use of quinazoline JAK inhibitors, including (3-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone; (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(3-fluorophenyl)methanone; (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanone; (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanone; (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(2-methoxyphenyl)methanone; (4-(1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanol; 2-(fluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)quinazolin-4-amine; 2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine; 2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)quinazolin-4-amine; N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(difluoro(4-fluorophenyl)methyl)quinazolin-4-amine; 3-(2-(4-fluorobenzoyl)quinazolin-4-ylamino)-1H-pyrazole-5-carbonitrile; (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)methanol; 2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine; 2-(amino(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)quinazolin-4-amine; 3-(2-((4-fluorophenyl)(hydroxy)methyl)quinazolin-4-ylamino)-1H-pyrazole-5-carbonitrile; (5-fluoro-4-(5-methyl-1H-pyrazol-3-ylamino)quinazolin-2-yl)(4-fluorophenyl)methanol; (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)-7-(trifluoromethyl)quinazolin-2-yl)methanone; and (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)-7-(trifluoromethyl)quinazolin-2-yl)methanol. United States Patent No. 8,927,580 to Richardson et al. discloses the use of dipyridyl thiosemicarbazones such as di-2-pyridylketone 4-ethyl-4-methyl-3-thiosemicarbazone. United States Patent No. 8,927,562 to Meng et al. discloses the use of fused tricyclic inhibitors of mTOR. United States Patent No. 8,927,560 to Ahmed et al. discloses the use of 4-aza-2,3-didehydropodophyllotoxin compounds. United States Patent No. 8,927,548 to Ying et al. discloses the use of triazole compounds that are Hsp90 inhibitors. United States Patent No. 8,927,538 to Kamal et al. discloses the use of carbazole linked pyrrolo[2, 1-c][1,4]benzodiazepine hybrids as agents reacting with DNA to form an N2-guanine adduct that lies within the minor groove of duplex DNA via an

acid-labile aminal bond to the electrophilic imine at the N10-C11 position. United States Patent No. 8,927,533 to Giannini et al. discloses the use of lactam-substituted thio derivatives. United States Patent No. 8,921,565 to Flynn et al. discloses the use of pyridone amides as c-Met kinase inhibitors, such as N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-(2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-pivalamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-isobutyramidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide. United States Patent No. 8,921,522 to Kamal et al. discloses the use of benzothiazole derivatives including olefins, chalcones, pyrazolines, pyrazole, isoxazolines, and isoxazoles linked to 2-phenylbenzothiazoles. United States Patent No. 8,921,546 to Chao discloses the use of imidazothiazoles such as 7-(2-morpholin-4-yl-ethoxy)-2-(4-nitro-phenyl)imidazo[2,1-b][1,3]benzothiazole and 4-(7-(2-morpholinoethoxy)benzo[d]imidazo[2,1-b]thiazol-2-yl)aniline. United States Patent No. 8,921,414 to Reddell et al. discloses the use of spiroketals. United States Patent No. 8,921,407 to Ying et al. discloses the use of pyrazole compounds as Hsp90 modulators. United States Patent No. 8,921,367 to Friberg et al. discloses the use of AMG 900 (N-(4-(3-(2-aminopyrimidin-4-yl)pyridin-2-yloxy)phenyl)-4-(4-methylthiophen-2-yl)phthalazin-1-amine) as Aurora kinase inhibitor. United States Patent No. 8,920,799 to Graham et al. discloses the use of Axl ligand-binding portion of Axl tyrosine kinase receptor. United States Patent No. 8,778,340 to Dupont et al. discloses the use of anti-angiogenesis agents including antibodies. United States Patent No. 8,748,470 to Lengyel et al. (fatty acid binding protein inhibitors including carbazole butanoic acids, aryl sulfonamides, sulfonylthiophenes, 4-hydroxypyrimidines, 2,3-dimethylindoles, benzoylbenzenes, biphenyl-alkanoic acids, 2-oxazole-alkanoic acids, tetrahydropyrimidones, pyridones, pyrazinones, aryl carboxylic acids, tetrazoles, triazolopyrimidinones, indoles, BMS480404 ((2S)-2-[2,3-bis[(2-

chlorophenyl)methoxy]phenyl]-2-hydroxyacetic acid), or BMS309403 (2-[[2'-(5-ethyl-3,4-diphenyl-1*H*-pyrazol-1-yl)[1,1'-biphenyl]-3-yl]oxy]-acetic acid. United States Patent No. 8,541,433 to Clozel et al. discloses the use of macitentan. United States Patent No. 8,362,072 to Jensen et al. discloses the use of BRCA1 production enhancers. United States Patent No. 8,268,889 to Kloog et al. discloses the use of farnesylthiosalicylic acid and analogs. United States Patent No. 7,968,514 to Coelingh Bennink et al. discloses the use of immunogenic peptides. United States Patent No. 7,323,164 to Chandrasekher et al. discloses the use of interleukin 24. United States Patent No. 7,074,575 to Chandrasekher et al. discloses the use of interleukin 19. United States Patent No. 6,237,307 to Miller et al. discloses the use of 2-phenyl-1-[4-(2-aminoethoxy)-benzyl]-indole derivatives. United States Patent No. 5,597,798 to Howell et al. discloses the use of combinations with taxol and epidermal growth factor. United States Patent Application Publication No. 2014/0336150 by Frederick discloses the use of karenitecin (7-[(2′-trimethylsilyl)ethyl]-20(S) camptothecin). United States Patent Application Publication No. 2014/0315959 by Moore et al. discloses the use of benzylidinebenzohydrazides. United States Patent Application Publication No. 2014/0309184 by Rocconi et al. discloses the use of Smo inhibitors used in combination with other drugs, including platinum-containing agents. United States Patent Application Publication No. 2014/0302174 by Chan et al. discloses combination therapy with gemcitabine, cisplatin or carboplatin, and 5-[2-tert-butyl-5-(4-fluoro-phenyl)-1H-imidazol-4-yl]-3-(2,2-dimethyl-propyl)-3H-imidazo[4,5-b]pyridin-2-ylamine. United States Patent Application Publication No. 2014/0275174 by Moore et al. discloses the use of 2-amino-4H-naphtho[1,2-b]pyran-3-carbonitriles. United States Patent Application Publication No. 2014/0134169 by Kuhnert et al. discloses the use of Dll4 antagonists. United States Patent Application Publication No. 2013/0231286 by Chen discloses the use of prolactin receptor antagonist. United States Patent Application Publication No. 2013/0203861 by Liu et al. discloses the use of cyclohexenone compounds. United States Patent Application Publication No. 2012/0269827 by Whiteman et al. discloses the use of conjugates with CD56. United States Patent Application Publication No. 2012/0237502 by Darnowski discloses the use of 17,20-lyase inhibitors such as 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene, 6-[(7S)-7-hydroxy-6,7-dihydro-5H-

pyrrolo[1,2-c]imidazol-7-yl]-N-methyl-2-naphthalenecarboxamide, 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene, or 6-[(7S)-7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl]-N-methyl-2-naphthalenecarboxamide. United States Patent Application Publication No. 2012/0183546 by Weinreich discloses the use of angiopoietin-2 inhibitor. United States Patent Application Publication No. 2010/0009330 by Sherman et al. discloses the use of PARP inhibitors including 4-iodo-3-nitrobenzamide. United States Patent Application Publication No. 2009/0118271 by Umeda et al. discloses the use of water-soluble prodrugs such as (9S)-1-butyl-9-ethyl-9-hydroxy-1H,12H-pyrano[3′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-9-ethyl-9-hydroxy-1-[2-(4-morpholino)ethyl]-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-1-[3-(dimethylamino)propyl]-9-ethyl-9-hydroxy-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-9-ethyl-9-hydroxy-1-phenethyl-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-9-ethyl-9-hydroxy-1-[2-(pyridin-2-yl)ethyl]-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; (9S)-9-ethyl-1-heptyl-9-hydroxy-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione; and (9S)-9-ethyl-9-hydroxy-1-propyl-1H,12H-pyrano[3′′,4′′:6′,7′]indolizino[1′,2′:6,5]pyrido[4,3,2-de]quinazoline-2,10,13(3H,9H,15H)-trione. United States Patent Application Publication No. 2009/0099102 by Ye et al. discloses the use of ginkgolides, including ginkgolides A and B. United States Patent Application Publication No. 2007/0299020 by Zeldis discloses the use of 4-(amino)-2(2,6-dioxo(3-piperidyl)-isoindoline-1,3-dione. United States Patent Application Publication No. 2006/0058217 by White et al. discloses the use of antialamin. United States Patent Application No. 2005/0272766 by Koya et al. discloses the use of 1-glyoxylamide indolizines. These patents and patent application publications are incorporated herein in their entirety by this reference.

[0329] The invention is illustrated by the following Examples. These Examples are included for illustrative purposes only, and are not intended to limit the invention.

Example 1

In Vivo Efficacy of Dianhydrogalactitol in the Treatment of Non-Small-Cell Lung Cancer Employing a Mouse Xenograft Model

[0330] Background

[0331] The median overall survival time for patients with stage IV non-small cell lung cancer (NSCLC) is 4 months, and 1- and 5-year survival is less than 16% and 2%, respectively. NSCLC is usually treated with surgery followed by treatment with either Tyrosine Kinase Inhibitors (TKIs) (e.g., erlotinib, gefitinib) or platinum-based regimens (e.g. cisplatin). TKIs have resulted in vastly improved outcomes for patients with EGFR mutations; however, TKI resistance has emerged as a significant unmet medical need, and long-term prognosis with platinum-based therapies is poor. Additionally, the incidence of brain metastases is high in patients with NSCLC with a poor prognosis.

[0332] Dianhydrogalactitol is a structurally unique bi-functional alkylating agent mediating interstrand DNA crosslinks at targeting N^7 of guanine, thus differing in mechanism of action from TKIs and cisplatin. Dianhydrogalactitol further crosses the blood-brain barrier and accumulates in tumor tissue. Dianhydrogalactitol has demonstrated activity against NSCLC in preclinical and clinical trials, both as a single agent and in combination with other treatment regimens, suggesting dianhydrogalactitol may be a therapeutic option for drug-resistant NSCLC and NSCLC patients with brain metastasis.

[0333] The purpose of the study reported in this Example is to evaluate the activity of dianhydrogalactitol in *in vivo* models of drug-resistant NSCLC in comparison to other drugs, including cisplatin. Rag2 mice bearing subcutaneous human lung adenocarcinoma xenograft tumors of either TKI-resistant (H1975) or TKI-sensitive (A549) origin were treated.

[0334] Cell Lines and Animals

[0335] Two human NSCLC cell lines, A549 (TKI-sensitive) and H1975 (TKI-resistant), were used as xenograft tumor models in female Rag2 mice. The mice were

6 to 8 weeks of age and weighed 18-23 grams. 10 mice were used per group. The results reported below are for the A549 NSCLC cell line.

[0336] **Drugs**

[0337] Cisplatin was used in normal saline at a dose of 5 mg/kg. Administration was intravenous.

[0338] Dianhydrogalactitol was used in 0.9% sodium chloride for injection at 1.5 mg/kg to 6 mg/kg. Administration was intraperitoneal.

[0339] The study grouping was as shown in Table 1, below ("VAL-083" is dianhydrogalactitol).

Table 1

Study Grouping

Gp#	Group Name	No. mice	TA/CA* Dose (mg/kg)	Admin. Route	Volume (uL/20g)	Timepoint/ Schedule
1	Untreated control	10	-			
2	Cisplatin control	10	5	i.v.	200	Q7D X 3
3	VAL-083 dose 1	10	1.5	i.p.	200	M, W, F X 3
4	VAL-083 dose 2	10	3	i.p.	200	M, W, F X 3
5	VAL-083 dose 3	10	6	i.p.	200	M, W, F X 3

* TA: Test Article; CA: Control Article

[0340] Treatment was initated at a tumor volume of 100 mm^3 to 150 mm^3.

[0341] **Experimental Design**

[0342] *Cell Preparation and Tissue Culture*. The A549 human lung carcinoma cell line had been obtained from the American Type Culture Collection (Cat. # CCL-185). The cells were started from a frozen vial of lab stock that were frozen down from the ATCC original vial and kept in liquid nitrogen. Cell cultures with a passage number of 3 to 10 and a confluence of 80%-90% were used. Cells were grown in RPMI 1640 supplemented with 10% fetal bovine serum and 2 mL L-glutamine at 37° C in 5% CO_2 environment. Cells were subcultured once weekly with a split ratio 1:3 to 1:8 and expanded.

[0343] For cell preparation and harvesting for subcutaneous (s.c.) inoculation, the cells were rinsed briefly once with Hanks Balanced Salt Solution without calcium or magnesium. Fresh trypsin/EDTA solution (0.25% trypsin with tetrasodium EDTA) was added, the flask was laid horizontally to ensure that the cells were covered by

trypsin/EDTA, and the extra trypsin/EDTA was aspirated. The cells were allowed to sit at 37°C for a few minutes. The cells were observed under an inverted microscope until the cell layer was dispersed, fresh medium was added, 50 μL of cell suspension was taken and mixed with trypan blue (1:1), and the cells were counted and cell viability assessed by using Cellometer Auto T4. The cells were centrifuged at 200 × g for 7 minutes and the supernatant was aspirated. The cells were resuspended in growth medium to obtain a concentration of 100×10^6 cells/mL. For inoculation, 5×10^6 cells were used in an injection volume of 50 μL per mouse in 1:1 Matrigel.

[0344] *Tumor Cell Implantation* On day 0, tumor cells were implanted subcutaneously into mice in a volume of 50 μL in Matrigel using a 28-gauge needle; injection of the tumor cells was in the back of the mice. Mice were randomly assigned to groups based on tumor volume. The means of the tumor volumes prior at the time of randomization were 89.15 mm^3, 86.08 mm^3, 95.49 mm^3, 87.15 mm^3 and 81.76 mm^3 for groups 1-5, respectively.

[0345] *Dose Administration* Dianhydrogalactitol (DAG) was provided as a lyophilized product at 40 mg of DAG per vial. For administration, 5 mL of 0.9% sodium chloride for injection, USP (saline) was added to yield a DAG solution with a concentration of 8 mg/mL. This stock solution was stable for 4 hours at room temperature or for 24 hours at 4° C. Further dilutions were made to prepare solutions of injection of 0.9 mg/mL (for administration of 0.18 mg/mouse in 0.2 mL; diluted from the 8 mg/mL reconstituted solution); of 0.45 mg/mL (for administration of 0.09 mg/mouse in 0.2 mL; a 1 to 2 dilution of the 0.9 mg/mL solution); and of 0.225 mg/mL (for administration of 0.045 mg/mouse in 0.2 mL; a 1 to 2 dilution of the 0.45 mg/mL solution).

[0346] *Intravenous Injections* Mice were injected with the required volume to administer the prescribed dose (mg/kg) to the animals based on individual mouse weights using a 28-gauge needle. The injection volume was 200 μL for a 20-g mouse. The mice were briefly (less than 30 seconds) restrained during intravenous injections. Dilation of the vein for intravenous injections was achieved by holding the animals under a heat lamp for a period of between 1-2 minutes.

[0347] *Intraperitoneal Injections* Mice were individually weighed and injected intraperitoneally according to body weight at the specified injection concentration (see Table 1). The injection volume was based on 200 μL per 20-g mouse. The abdominal surface was wiped down with 70% isopropyl alcohol to clean the injection site.

[0348] **Data Collection**

[0349] *Tumor Monitoring* Tumor growth was monitored by measuring tumor dimensions with calipers beginning on the first day of treatment. Tumor length and width measurements were obtained each Monday, Wednesday, and Friday. Tumor volumes were calculated according to the equation $L \times W^2/2$ with the length (in mm) being defined as the longer axis of the tumor. Animals were weighed at the time of tumor measurement. Tumors were allowed to grow to a maximum of 800 mm^3 before termination.

[0350] All animals had blood collected by cardiac puncture at termination for CBC (complete blood count) with differentiation. Statistical significance ($p<0.05$) between untreated control and groups 4 or 5 (dianhydrogalactitol-treated groups) was found for hemoglobin (g/L) for CBC analysis. Differential analysis was performed; however, it is noted that even in control mice there are low white blood cell (WBC) numbers (due to the fact that the strain is immunocompromised, which would affect WBC production). For WBC, statistical significance ($p<0.05$) was observed for lymphocytes and eosinophils. There were no differences between control non-tumor bearing animals (mouse ID # control 1 and control 2) and untreated control tumor-bearing animals (group 1; mouse ID # 1-10) for CBC/differential analyses.

[0351] **Observations of Animals**

[0352] *Clinical Observations* All animals were observed post-administration, and at least once per day, more frequently if deemed necessary, during the pre-treatment and treatment periods for morbidity and mortality. In particular, signs of ill-health were based on body weight loss, change in appetite, and behavioral signs such as altered gait, lethargy, and gross manifestations of stress. If signs of severe toxicity or tumor-related illness were seen, the animals were terminated by isoflurane overdose followed by CO_2 asphyxiation, and a necropsy was performed to assess other signs of

toxicity. The following organs were examined: liver, gall bladder, spleen, lung, kidney, heart, intestine, lymph nodes, and bladder. Any unusual findings were noted.

[0353] The methodology was reviewed and approved by the Institutional Animal Care Committee (IACC) at the University of British Columbia. The housing and use of animals were performed in accordance with the Canadian Council on Animal Care Guidelines.

[0354] Summaries for the administration of dianhydrogalactitol ("VAL-083") and cisplatin are shown in Tables 2-3, below:

Table 2

Administration of Dianhydrogalactitol

GROUP#	TREATMENT	DOSE mg/kg	MICE /group	AVR.WT. g	CONC. mg/ml	INJECTED ml/20g	TOTAL ml	TOTAL mg	STOCK ml	SALINE ml
VAL-083 Stock conc.	6.86 *	mg/ml								
3	VAL-083	1.5	10	20.0	0.150	0.200	3.00	0.450	0.563	2.438
4	VAL-083	3.0	10	20.0	0.300	0.200	3.00	0.900	1.125	1.875
5	VAL-083	6.0	10	20.0	0.600	0.200	3.00	1.800	2.250	0.750
						Total:	9.00	3.150	3.938	

Table 3

Administration of Cisplatin

Group #	Treatment	Dose, mg/kg	Mice/Group	Average Weight, g	Conc., mg/mL	Injected, ml/20 g	Total, mL	Total, mg	Stock. mL	Saline, mL
Cisplatin Control	Cisplatin	5.0	10	20.0	0.500	0.200	3.00	1.500	1.500	1.500

[0355] **Results and Conclusion**

[0356] The results are shown in Figures 1-2.

[0357] Figure 1 is a graph that shows body weight of female Rag2 mice after subcutaneous inoculation with 5 million A549 cells. Body weight is shown on the y-axis versus days post-inoculation on the x-axis for the results of the Example. In Figures 1-2 of the Example, • is the untreated control; ■ is the cisplatin control; ▲ is

dianhydrogalactitol at 1.5 mg/kg; ▲ is dianhydrogalactitol at 3.0 mg/kg; and ♦ is dianhydrogalactitol at 6.0 mg/kg.

[0358] According to the results of Figure 1, body weight loss was observed in mice treated with 5 mg/kg cisplatin (group 2) and 6 mg/kg dianhydrogalactitol (group 5). Group 5 treatment was stopped after 3 doses due to significant body weight loss. Body weights are shown as means ± S.D.

[0359] Figure 2 is a graph that shows the tumor volume (means ± S.E.M.) for the A549 tumor-bearing female Rag2 mice with tumor volume on the y axis versus days post-inoculation on the x-axis for the results of the Example. The top panel of Figure 2 represents all mice for the complete duration of the study. The bottom panel of Figure 2 represents all mice until day 70 (last day for untreated control group).

[0360] To summarize the results, mice were administered with untreated control (group 1), cisplatin at 5 mg/kg Q7D × 3 i.v. (group 2) or dianhydrogalactitol at 1.5 mg/kg i.p. (group 3), 3 mg/kg (group 4), and 6 mg/kg (group 5) Monday, Wednesday, Friday for 3 weeks and tumor volume was measured 3 × weekly and summarized in Figure 2. The top panel indicates tumor volume for all animals and the bottom panel shows results for animal until day 70. Note that the number of animals remaining on study on day 70 was 2/10 (group 1), 6/10 (group 2), 7/10 (group 3), 6/10 (group 4) and 8/10 (group 5). For groups 1-5, a mean tumor volume of 200 mm^3 was observed on days 43, 49, 45, 42 and 54, respectively. For groups 1-4, a mean tumor volume of 400 mm^3 was reached on days 56, 66, 67 and 81 respectively. The doubling times for groups 1-4 were 13, 17, 22 and 39, respectively. A tumor growth delay of 26 days was observed in animals administered 3 mg/kg dianhydrogalactitol compared to untreated controls. The positive control of 5 mg/kg cisplatin had a tumor growth delay of only 4 days in comparison.

[0361] In terms of the tolerability of the dosages, dianhydrogalactitol at 6 mg/kg resulted in significant weight loss and morbidity of the mice and only 3 of the 9 scheduled doses were administered. The 5 mg/kg dose of cisplatin may also be near the MTD as 1 mouse was unable to receive the last dose.

[0362] In conclusion, administration of dianhydrogalactitol at a dose of 3 mg/kg resulted in a significant tumor growth delay as compared to cisplatin at 5 mg/kg.

Example 2

Use of Dianhydrogalactitol as a Novel Treatment Option for Chemo-Resistant Non-Small-Cell Lung Cancer

[0363] The WHO predicts that the incidence of lung cancer may exceed 1 million cases per year by 2025 with non-small cell lung cancer (NSCLC) representing up to 90% of newly diagnosed cases. The median overall survival time for patients with stage IV NSCLC is 4 months, while 1- and 5-year survival is less than 16% and 2%, respectively. Metastatic NSCLC is usually treated with either Tyrosine Kinase Inhibitors (TKIs) (e.g. gefitinib) or platinum-based regimens (e.g. cisplatin). TKIs have resulted in vastly improved outcomes for patients with EGFR mutations; however, TKI resistance has emerged as a significant unmet medical need, and long-term prognosis with platinum-based therapies is poor. Additionally, the incidence of brain metastases is high in patients with NSCLC with a poor prognosis. In particular, NSCLC represents approximately 90% of the lung cancer cases diagnosed in China.

[0364] Dianhydrogalactitol is a structurally unique bi-functional alkylating agent mediating interstrand DNA crosslinks targeting N7 of guanine, thus differing in mechanism from TKIs and cisplatin. Dianhydrogalactitol is approved for treatment of lung cancer in China and has documented activity against NSCLC in historical NCI-sponsored clinical trials in the United States; however, specific questions regarding the efficacy of dianhydrogalactitol in comparison to cisplatin and in TKI-resistant NSCLC have to our knowledge not been addressed before. Further, dianhydrogalactitol crosses the blood-brain barrier and accumulates in tumor tissue. Dianhydrogalactitol has demonstrated activity against NSCLC in preclinical and clinical trials, suggesting dianhydrogalactitol may be a therapeutic option for drug-resistant NSCLC and NSCLC patients with brain metastasis. When tested side-by-side in a standard syngeneic mouse fibrosarcoma model (RIF-1 cell-line in C3H mice), dianhydrogalactitol demonstrated superiority to cisplatin in tumor growth delay. For mice treated with a single IP injection of dianhydrogalactitol (10 mg/kg) tumor growth was delayed by 5.6 days compared to control, versus 1.5 days for mice treated with single dose cisplatin (4 mg/kg). Combination treatment of dianhydrogalactitol and cisplatin produced a more than additive effect by delaying growth 8.7 days.

[0365] Previous clinical studies showing dianhydrogalactitol activity in NSCLC combined with the new data on synergy with cisplatin, makes dianhydrogalactitol a promising alternative for NSCLC with brain metastases as well as chemo-resistant NSCLC.

[0366] *In vitro*, the cytotoxic effect of dianhydrogalactitol in combination with cisplatin or oxaliplatin was tested in NSCLC cell-lines A549 and H1975. The results show additive and more than additive effects of combining dianhydrogalactitol with cisplatin or oxaliplatin in both cell-lines.

[0367] *In vivo*, in two separate studies we evaluated the activity of dianhydrogalactitol in in vivo models of EGFR-TKI-resistant NSCLC in comparison to cisplatin. Rag2 mice bearing subcutaneous human lung adenocarcinoma xenograft tumors of either TKI-sensitive (A549) or TKI-resistant (H1975) origin were treated. Dianhydrogalactitol was given i.p. 3 times/week for 3 weeks, and the in vivo efficacy of dianhydrogalactitol in controlling tumor growth compared to cisplatin (5 mg/kg). Saline was used as control treatment. Disease progression was evaluated by tumor volume, clinical observations and body weight measurements. Blood samples were analyzed for CBC/differential analyses to assess myelosuppression or other changes in blood chemistry.

[0368] For A549 cells, tumor growth delay of 26 days was observed in animals treated with 3 mg/kg dianhydrogalactitol compared to controls, versus a 4-day delay for mice treated with cisplatin. Mean tumor volume on day 68 was significantly reduced in animals treated with 3 mg/kg dianhydrogalactitol compared to controls ($p=0.001$).

[0369] For H1975 cells, treatment was stopped after 6 doses of dianhydrogalactitol in the 4 mg/kg group due to significant body weight loss and the mice quickly recovered. Median survival time in mice treated with 4 mg/kg dianhydrogalactitol was 41 days compared to 31 days for all other treatment and control groups. Mean tumor volume on day 31 was significantly reduced in animals treated with 4 mg/kg dianhydrogalactitol compared to control ($p=0.004$).

[0370] **Methods**

[0371] *In Vivo* Models

[0372] Cell number for inoculation was 5×10^6 cells for A549 cells in an injection volume of 50 μL per animal. For H1975 cells, cell number for inoculation was 2×10^6 cells in an injection volume of 50 μL per animal.

[0373] Treatment was initiated at average tumor volume of 100-150 mm^3.

Table 4

Treatment Protocol for Testing Efficacy of Dianhydrogalactitol

Group Name	Dosage (mg/kg), A549	Dosage (mg/kg), H1975	No. Mice	Admin. Route	Volume (μL/20 g)	Timepoint Schedule
1. Untreated			10	n/a	n/a	n/a
2. Cisplatin	5.0	5.0	10	i.v.	200	Q7D × 3
3. Dianhydrogalactitol	1.5	2.0	10	i.p.	200	M, W, F × 3
4. Dianhydrogalactitol	3.0	3.0	10	i.p.	200	M, W, F × 3
5. Dianhydrogalactitol	6.0	4.0	10	i.p	200	M, W, F × 3

[0374] Body weight loss was observed in mice treated with 5 mg/kg cisplatin (group 2) and 4 mg/kg dianhydrogalactitol (group 5). Treatment was stopped after 6 doses of dianhydrogalactitol in the 4 mg/kg group due to significant body weight loss, and the mice then quickly recovered.

[0375] *In Vitro Models*

[0376] The *in vitro* activity of dianhydrogalactitol in combination with cisplatin was tested in NSCLC cell-lines A549 and H1975. Cells were treated with dianhydrogalactitol and cisplatin or oxaliplatin, simultaneously, using IC10-30 concentrations of the individual agents, and cytotoxicity was monitored on day 5 with the colorimetric MTT assay. P-values were calculated by Student's t-test analysis of experimental values vs. predicted additive values for the treatment combinations

[0377] Tumor growth inhibition (TGI) was calculated according to Equation (1):

$$TGI = \frac{(TVcontrolDay68\text{-}TVcontrol,int)\text{-}(TVtxDDay68\text{-}TVtx, int) \times 100\%}{(TVcontrolDay68\text{-}TVcontrol, int.)} \quad (1).$$

[0378] Tumor growth delay (TGD) was calculated according to Equation (2):

$$TGD = DTtx - DTcontrol \quad (2).$$

[0379] For these calculations, TV is tumor volume, tx is treatment, int is initial, DT is doubling time for mean tumor volume from 200 mm^3 to 400 mm^3 for A549 or from 300 mm^3 to 600 mm^3 for H1975. MTV is mean tumor volume in mm^3 and TCR is tumor control ratio.

[0380] **Results**

[0381] The results for A549, which are TKI-sensitive cells, are shown in Table 5 and Figure 3. A significant survival benefit was observed with dianhydrogalactitol at 3mg/kg as shown in Figure 3 and Table 5. Figure 3 is a Kaplan-Meier survival plot in an in vivo model of A549 (TKI-sensitive) cells in female Rag2 mice comparing the effect of cisplatin at 5 mg/kg and dianhydrogalactitol at 1.5 mg/kg and 3.0 mg/kg for A549 (TKI-sensitive) cells. A log-rank statistical test (Mantel-Cox) was performed indicating p value of 0.0446 indicating a significant difference between the survival curves. A tumor growth delay of 26 days was observed in animals treated with 3 mg/kg dianhydrogalactitol compared to untreated controls, versus positive control, 5 mg/kg cisplatin, which resulted in a tumour growth delay of 4 days compared to untreated controls. Mean tumor volume on day 68 was significantly reduced in animals treated with 3 mg/kg dianhydrogalactitol (p=0.001) compared to untreated control. These observations suggest that dianhydrogalactitol maintains activity where cisplatin fails to gain a statistically significant benefit.

Table 5

Analysis Parameters for Groups 1-4 in A549 Model

Treatment	MTV* at Day 68	TCR* at Day 68	TGD (Days)	TGI (%)	P value**	Median survival (days)
Control	638	1	0	0	n/a	69
Cisplatin, 5 mg/kg	460	0.72	4	29%	0.059	72
Dianhydrogalactitol, 1.5 mg/kg	440	0.69	9	32%	0.069	73.5
Dianhydrogalactitol, 3 mg/kg	303	0.47	26	55%	0.001	82

[0382] ** shows the results for the unpaired *t*-test of tumor volume on day 68, treatment compared to untreated control.

[0383] The results for H1975, which are TKI-resistant cells, are shown in Table 6 and Figure 4. A significant survival benefit was observed with dianhydrogalactitol at 4mg/kg as shown in Figure 4 and Table 6. Figure 4 is a Kaplan-Meier survival plot in an in vivo model of H1975 (TKI-resistant) cells in female Rag2 mice comparing the effect of cisplatin at 5 mg/kg and dianhydrogalactitol at 2 mg/kg, 3 mg/kg, and 4 mg/kg for H1975 (TKI-resistant) cells. The median survival time for mice treated with 4 mg/kg dianhydrogalactitol was 41 days compared to 31 days for all other treatment and control groups. A log-rank statistical test (Mantel-Cox) was performed indicating p value of 0.0009 indicating a significant difference between the survival curves. Mean tumor volume on day 31 was significantly reduced in animals treated with 4 mg/kg dianhydrogalactitol compared to control (p=0.004). These observations suggest that dianhydrogalactitol maintains activity where cisplatin fails to gain a statistically significant benefit, even in a TKI-resistant setting.

Table 6

Analysis Parameters for Groups 1-5 in H1975 Model

Treatment	MTV* at Day 31	TCR* at Day 31	P value**	Median survival (days)
Control	459	1	n/a	31
Cisplatin, 5 mg/kg	381	0.83	0.102	31
Dianhydrogalactitol, 2 mg/kg	396	0.87	0.490	31
Dianhydrogalactitol, 3 mg/kg	383	0.84	0.769	31
Dianhydrogalactitol, 4 mg/kg	262	0.57	0.404	41

[0384] ** shows the results for the unpaired *t*-test of tumor volume on day 31, treatment compared to untreated control.

[0385] In a separate, standard *in vivo* model of anti-cancer activity, VAL-083 was superior to cisplatin in tumor growth delay. Mice were treated with a single IP injection of either cisplatin, dianhydrogalactitol, or dianhydrogalactitol followed immediately by cisplatin. Interestingly, combination treatment of dianhydrogalactitol with cisplatin produced a more than additive effect by delaying growth 8.65 days, when tested side-by-side in a standard syngeneic mouse fibrosarcoma model (RIF-1 cell-line in C3H mice). The results are shown in Table 7.

Table 7

Treatment	Dose (mg/kg)	Days to 4 × Median Tumor Size	Tumor Delay (days)
Untreated	n/a	6.29	0.00
Cisplatin	4	7.75	1.45
Dianhydrogalactitol	10	11.45	5.16
Dianhydrogalactitol + Cisplatin	10 + 4	14.94	8.65

[0386] Additional *in vitro* studies were performed to investigate the cytotoxic effect of dianhydrogalactitol alone or in combination with cisplatin (A) or oxaliplatin (B). Figure 5 shows the cytotoxic effect of dianhydrogalactitol alone or in combination with cisplatin (Figure 5A) or oxaliplatin (Figure 5B) on A549 NSCLC cells *in vitro*. Data are shown as mean ± SE. Figure 6 shows the cytotoxic effect of dianhydrogalactitol alone

or in combination with cisplatin (Figure 6A) or oxaliplatin (Figure 6B) on H1975 NSCLC cells *in vitro*. Data are shown as mean ± SE.

[0387] Dianhydrogalactitol in combination with either cisplatin or oxaliplatin has a more than additive cytotoxic effect on both TKI-resistant (H1975) and TKI-sensitive (A549) NSCLC cells. These results support the potential for synergistic benefit for a combination of dianhydrogalactitol and platinum-based therapies, similar to those results observed *in vivo.*

[0388] Taken together, the results suggest that dianhydrogalactitol is superior to cisplatin in both TKI-sensitive and TKI-resistant tumor models, has synergistic effect in combination with cisplatin, and suggest clinical potential in TKI-resistant NSCLC. In particular, dianhydrogalactitol maintains activity under conditions where platinum-based regimens have little or effect. Additionally, dianhydrogalactitol has a super-additive effect when combined with cisplatin or oxaliplatin in both TKI-sensitive (A549) and TKI-resistant (H1975) NSCLC cell-lines *in vitro*. Moreover, dianhydrogalactitol with cisplatin is better than additive *in vivo*.

[0389] Taken together, these results support dianhydrogalactitol as a viable treatment option for NSCLC patients failing platinum-based and TKI-based therapy, and support the potential benefit as part of a platinum-based combination therapy in newly diagnosed patients.

Example 3

Further Results on Cell Lines

[0390] Background

[0391] The median overall survival time for patients with stage IV non-small cell lung cancer (NSCLC) is 4 months, and 1- and 5-year survival is less than 16% and 2%, respectively. NSCLC is usually treated with surgery followed by treatment with either Tyrosine Kinase Inhibitors (TKIs) or platinum-based regimens (e.g. cisplatin). TKIs have resulted in vastly improved outcomes for patients with EGFR mutations; however, TKI resistance has emerged as a significant unmet medical need, and long-term prognosis with platinum-based therapies is poor. Dianhydrogalactitol is a structurally unique bifunctional alkylating agent mediating interstrand DNA crosslinks at N^7 of guanine, thus

differing in mechanism of action from TKIs and cisplatin. Dianhydrogalactitol has demonstrated activity against NSCLC in preclinical and clinical trials, suggesting dianhydrogalactitol may be a therapeutic option for drug-resistant NSCLC. Dianhydrogalactitol is approved for treatment of lung cancer in China; however, specific questions regarding the efficacy of dianhydrogalactitol in comparison to - and combination with - cisplatin and in TKI-resistant NSCLC have to our knowledge not yet been investigated. The purpose of this study was to investigate dianhydrogalactitol activity in comparison to - and in combination with - cisplatin in TKI-resistant and TKI-sensitive NSCLC.

[0392] **Methods**

[0393] The *in vitro* activity of dianhydrogalactitol in combination with cisplatin was tested in NSCLC cell line H460. Cells were treated with dianhydrogalactitol and cisplatin, simultaneously, in a range of concentrations according to the Compusyn constant-ratio protocol and cytotoxicty was monitored on day 5 with the colorimetric MTT assay. The *in vivo* activity of dianhydrogalactitol compared to cisplatin was tested in Rag2 mice bearing xenograft tumors of either TKI-sensitive (A549) or TKI-resistant (H1975) origin.

[0394] Two human NSCLC cell lines, A549 and H1975, were used for subcutaneous human lung adenocarcinoma tumors and dianhydrogalactitol was given *i.p.* 3 times/week for 3 weeks. Disease progression was evaluated by tumor volume, clinical observations and body weight measurements.

[0395] **Results**

[0396] For H460, preliminary results indicate that the cytotoxic activity was more than additive for combinations of dianhydrogalactitol + cisplatin (Combination Index <0.7).

[0397] For A549, mean tumor volume on day 68 was significantly reduced in animals treated with 3 mg/kg dianhydrogalactitol ($p=0.001$) compared to untreated control. A tumor growth delay of 26 days was observed in animals treated with 3 mg/kg dianhydrogalactitol compared to untreated controls. Positive control, 5 mg/kg cisplatin, resulted in a tumor growth delay of 4 days compared to untreated controls.

[0398] For H1975, mean tumor volume on day 31 was significantly reduced in animals treated with 4 mg/kg dianhydrogalactitol (p=0.004) compared to untreated control. Median survival time for mice treated with 4 mg/kg dianhydrogalactitol was 41 days compared to 31 days for both 5 mg/kg cisplatin and for the untreated controls.

[0399] **Conclusions**

[0400] In conclusion, dianhydrogalactitol is highly efficacious in the NSCLC xenograft models, and preliminary *in vitro* studies suggest that dianhydrogalactitol in combination with cisplatin has synergistic activity.

Example 4

Dianhydrogalactitol Possesses Cytotoxic Activity Against Ovarian Cancer Lines

[0401] Dianhydrogalactitol possesses substantial cytotoxic activity against ovarian cancer cell lines.

[0402] Figure 7 is a graph showing a dose-response curve in an ovarian tumor cell line panel treated with dianhydrogalactitol *in vitro*. The ovarian tumor panel lines are as follows: • is A2780; ■ is 2780-CP16; ▲ is OVCAR-10; ▼ is HEY; and ♦ is OVCA-433. Dose-reponse curves were undertaken using a 5-day MTT assay to determine cell viability. The A2780 represents a cisplatin-sensitive model, whereas the other four cell lines are cisplatin-resistant. The cell line 2780-CP16 was derived for cisplatin resistance from A2780. The properties of some of these cell lines are disclosed in G.S. Hagopian et al., "Expression of *p53* in Cisplatin-Resistant Ovarian Cell Lines: Modulation with the Novel Platinum Analog (*1R*, *2R*-Diaminocyclohexane)(*trans*-diacetato)(dichloro)-platinum(IV)," Clin. Cancer Res. 5: 655-663 (1999), and in Z.H. Siddik et al., "Independent Pathways of p53 Induction by Cisplatin and X-Rays in a Cisplatin-Resistant Cell Line," Cancer Res. 58: 698-703 (1998), both incorporated herein by this reference.

[0403] The data of Figure 7 are shown in Table 8 in terms of the IC_{50} of dianhdrogalactitol in the wild-type p53 human ovarian tumor panel.

Table 8

IC_{50} of Dianhydrogalactitol in a Wild-Type p53 Human Ovarian Tumor Panel

Ovarian Tumor Models		
wt-p53	DAG IC_{50} (μM)	
Cell Line	Mean	SE
A2780	0.54	0.046
2780-CP	2.2	0.289
Ovcar-10	3.6	0.173
Hey	2.1	0.289
OVCA-433	2.3	0.058
N = 3		

[0404] Figure 8 is a graph showing the cytotoxicity of dianhydrogalactitol ("DAG"), cisplatin ("cis-Pt") and oxaliplatin ("Oxali-Pt") in a wild-type p53 human ovarian tumor panel *in vitro*. The relative activity (IC_{50}) of dianhydrogalactitol, cisplatin, and oxaliplatin against wild-type p53 ovarian tumor cells is shown.

[0405] Figure 9 is a graph showing the resistance factors of dianhydrogalactitol and the platinum drugs cisplatin and oxaliplatin in a wild-type p53 human ovarian tumor panel *in vitro*; the resistance factors are shown versus A2780. The activity of dianhydrogalactitol and the platinum drugs was normalized relative to the sensitive A2780 model. The graph indicates that the resistant tumor models are 10- to 30-fold resistant to cisplatin, 2- to 5-fold resistant to oxaliplatin, and 4- to 7-fold resistant to dianhydrogalactitol. Thus, cisplatin-resistant wild-type p53 ovarian tumor models demonstrate only partial cross-resistance to oxaliplatin and dianhydrogalactitol.

[0406] Therefore, the conclusion of this Example is that, even in ovarian tumors that demonstrate substantial resistance to cisplatin, dianhydrogalactitol exhibits a significant cytotoxic effect.

Example 5

Cytotoxicity Studies on NSCLC Tumor Models

[0407] Table 9 shows the cytotoxicity of dianhydrogalactitol (DAG) and the platinum drugs cisplatin and oxaliplatin in a number of cell lines for human NSCLC. The cell lines include cell lines with wild-type p53, cell lines with mutant p53, and cell lines in which p53 has been knocked out ("null"). The properties of these cell lines are

described in F. Bunz et al., "Requirement for p53 and p21 to Sustain G_2 Arrest After DNA Damage," Science 282: 1497-1501 (1998), incorporated herein by this reference.

Table 9

NSCLC Tumor Models							
		IC50 (uM)					
		Cisplatin		Oxaliplatin		DAG	
Cell Line	p53 Status	Mean	SE	Mean	SE	Mean	SE
H460	wt	0.45	0.092	0.36	0.034	0.49	0.050
A549	wt	0.74	0.106	0.57	0.059	1.76	0.314
H838	wt	1.18	0.092	2.63	0.041	4.62	0.421
H226	wt	1.82	0.156	0.82	0.023	6.11	0.984
H1975	mu	0.45	0.049	0.51	0.031	0.50	0.152
SkLU1	mu	0.89	0.019	2.02	0.473	2.72	0.022
H2122	mu	1.07	0.123	1.42	0.066	2.84	0.304
H157	mu	2.16	0.136	2.01	0.128	4.48	0.415
H1299	null	1.20	0.073	0.84	0.037	2.37	0.120

N = 3

[0408] Figure 10 is a graph showing the cytotoxicity of cisplatin and relative resistance in a human NSCLC tumor panel *in vitro*. The cell lines used are H460, A549, H838, and H226, which have a wild-type p53; H1975, SkLU1, H2122, and H157, which have a mutated p53; and H1229, which has a null p53. H460 is considered sensitive to cisplatin; the other cell lines are considered resistant to cisplatin, with the exception of H1975. Some are relatively more sensitive to oxaliplatin.

[0409] Figure 11 is a graph showing the cytotoxicity of oxaliplatin and relative resistance in a human NSCLC tumor panel *in vitro*. The cell lines used are H460, A549, H838, and H226, which have a wild-type p53; H1975, SkLU1, H2122, and H157, which have a mutated p53; and H1229, which has a null p53.

[0410] Figure 12 is a graph showing the cytotoxicity of DAG and relative resistance in a human NSCLC tumor panel *in vitro*. The cell lines used are H460, A549, H838, and H226, which have a wild-type p53; H1975, SkLU1, H2122, and H157, which have a mutated p53; and H1229, which has a null p53.

[0411] Figure 13 is a graph showing the cytotoxicity of dianhydrogalactitol ("DAG") and the platinum drugs cisplatin ("cis-Pt") and oxaliplatin ("Oxali-Pt") against engineered HCT-116 tumor models *in vitro*. To better explore dependency of activity on p53 status, the molecularly engineered colorectal HCT-116 models were used. These isogenic models were molecularly engineered to knockout p53 ($p53^{-/-}$) or p21 ($p21^{-/-}$).

The $p53^{+/+}$ or $p21^{+/+}$ represent the corresponding control. The $p53^{-/-}$ cell lines are described in J. Boyer et al., "Characterization of p53 Wild-Type and Null Isogenic Colorectal Cell Lines Resistant to 5-Fluorouracil, Oxaliplatin, and Irinotecan," Clin. Cancer Res. 10: 2158-2167 (2004), incorporated herein by this reference. The $p21^{-/-}$ cell lines are described in Z. Han et al., "Role of p21 in Apoptosis and Senescence of Human Colon Cancer Cells Treated with Camptothecin," J. Biol. Chem. 277: 17154-17160 (2002), incorporated herein by this reference. These IC_{50} values were used to determine resistance of knockout models relative to corresponding controls.

[0412] Figure 14 is a graph showing the resistance factors for dianhydrogalactitol ("DAG") and the platinum drugs cisplatin ("cis-Pt") and oxaliplatin ("Oxali-Pt") in engineered HCT-116 tumor models *in vitro*. The resistance factors in the engineered colorectal HCT-116 models demonstrate that loss of p53 and p21 result in about 2-fold or greater resistance to cisplatin and oxaliplatin, but the resistance to DAG was lower ($p53^{-/-}$) or non-existent ($p21^{-/-}$).

[0413] Figure 15 shows the combination index of dianhydrogalactitol ("DAG") with cisplatin or oxaliplatin *in vitro* in a human A549 NSCLC model.

[0414] Figure 16 is a graph showing the effect of dianhydrogalactitol (DAG) in combination with cisplatin or oxaliplatin on cytotoxicity in A549 cells *in vitro*. The left panel shows the results of DAG in combination with cisplatin; the right panel shows the results of DAG in combination with oxaliplatin.

[0415] Figure 17 is a graph showing the effect of dianhydrogalactitol (DAG) in combination with cisplatin or oxaliplatin on cytotoxicity in H460 cells *in vitro*. The left panel shows the results of DAG in combination with cisplatin; the right panel shows the results of DAG in combination with oxaliplatin. With N=3 independent studies with H460 cells, the combination of cisplatin + DAG almost reaches significance for super-additivity, whereas the combination of oxaliplatin + DAG is super-additive. Data are shown as Mean +/- SE.

[0416] Figure 18 is a graph showing the effect of dianhydrogalactitol (DAG) in combination with cisplatin or oxaliplatin on cytotoxicity in H1975 cells *in vitro*. The left panel shows the results of DAG in combination with cisplatin; the right panel shows the results of DAG in combination with oxaliplatin. With N=3 independent studies with

H1975 cells, the combination of cisplatin + DAG is additive, whereas the combination of oxaliplatin + DAG approaches significance for super-additivity. Data are shown as Mean +/- SE.

[0417] The results of this Example indicate that not only is dianhydrogalactitol an effective cytotoxic agent in a range of NSCLC tumor model cell lines, including cell lines that have mutated or absent p53 genes, but it is also effective in tumor model cell lines that have absent p21 genes. Furthermore, dianhydrogalactitol exhibits significant additive effects in terms of cytotoxicity with cisplatin and oxaliplatin, with super-additivity being observed with oxaliplatin.

ADVANTAGES OF THE INVENTION

[0418] The present invention provides improved methods and compositions employing dianhydrogalactitol for the treatment of non-small-cell lung carcinoma (NSCLC), a type of lung cancer that has proven resistant to chemotherapy by conventional means, as well as for the treatment of ovarian cancer.

[0419] The use of dianhydrogalactitol to treat NSCLC or ovarian cancer is expected to be well tolerated and not to result in additional side effects. Dianhydrogalactitol can be used together with radiation or other chemotherapeutic agents. Additionally, dianhydrogalactitol can be used to treat brain metastases of NSCLC or ovarian cancer and can be used to treat NSCLC or ovarian cancer in patients who have developed resistance to platinum-based therapeutic agents such as cisplatin, to tyrosine kinase inhbitors (TKIs), or to temozolomide.

[0420] Methods according to the present invention possess industrial applicability for the preparation of a medicament for the treatment of NSCLC or ovarian cancer. Compositions according to the present invention possess industrial applicability as pharmaceutical compositions.

[0421] The method claims of the present invention provide specific method steps that are more than general applications of laws of nature and require that those practicing the method steps employ steps other than those conventionally known in the art, in addition to the specific applications of laws of nature recited or implied in the claims, and thus confine the scope of the claims to the specific applications recited

therein. In some contexts, these claims are directed to new ways of using an existing drug.

[0422] The inventions illustratively described herein can suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising," "including," "containing," etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the future shown and described or any portion thereof, and it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions herein disclosed can be resorted by those skilled in the art, and that such modifications and variations are considered to be within the scope of the inventions disclosed herein. The inventions have been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the scope of the generic disclosure also form part of these inventions. This includes the generic description of each invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised materials specifically resided therein.

[0423] In addition, where features or aspects of an invention are described in terms of the Markush group, those schooled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. It is also to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those of in the art upon reviewing the above description. The scope of the invention should therefore, be determined not with reference to the above description, but should instead be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references, including patent publications, are incorporated herein by reference.

What is claimed is:

1. A method to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of a malignancy selected from the group consisting of non-small-cell lung carcinoma (NSCLC) and ovarian cancer comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the administration of the substituted hexitol derivative for treatment of NSCLC or ovarian cancer; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the substituted hexitol derivative for treatment of NSCLC or ovarian cancer.

2. The method of claim 1 wherein the substituted hexitol derivative is selected from the group consisting of galactitols, substituted galacitols, dulcitols, and substituted dulcitols.

3. The method of claim 2 wherein the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol.

4. The method of claim 3 wherein the substituted hexitol derivative is dianhydrogalactitol.

5. The method of claim 1 wherein the malignancy is NSCLC.

6. The method of claim 1 wherein the malignancy is ovarian cancer.

7. The method of claim 1 wherein the factor or parameter is selected from the group consisting of:

(a) dose modification;

(b) route of administration;

(c) schedule of administration;

(d) administration to promote preferential accumulation in brain tissue;

(e) selection of disease stage;

(f) patient selection;

(g) patient/disease phenotype;

(h) patient/disease genotype;

(i) pre/post-treatment preparation

(j) toxicity management;

(k) pharmacokinetic/pharmacodynamic monitoring;

(l) drug combinations;

(m) chemosensitization;

(n) chemopotentiation;

(o) post-treatment patient management;

(p) alternative medicine/therapeutic support;

(q) bulk drug product improvements;

(r) diluent systems;

(s) solvent systems;

(t) excipients;

(u) dosage forms;

(v) dosage kits and packaging;

(w) drug delivery systems;

(x) drug conjugate forms;

(y) compound analogs;

(z) prodrugs;

(aa) multiple drug systems;

(ab) biotherapeutic enhancement;

(ac) biotherapeutic resistance modulation;

(ad) radiation therapy enhancement;

(ae) novel mechanisms of action;

(af) selective target cell population therapeutics;

(ag) use with ionizing radiation;

(ah) use with an agent that counteracts myelosuppression; and

(aj) use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier to treat brain metastases of NSCLC.

8. The method of claim 7 wherein the substituted hexitol derivative is dianhydrogalactitol.

9. The method of claim 7 wherein the improvement is made by dose modification and the dose modification is at least one dose modification selected from the group consisting of:

(i) continuous i.v. infusion for hours to days;

(ii) biweekly administration;

(iii) doses greater than 5 mg/m^2/day;

(iv) progressive escalation of dosing from 1 mg/m^2/day based on patient tolerance;

(v) use of caffeine to modulate metabolism;

(vi) use of isoniazid to modulate metabolism;

(vii) selected and intermittent boosting of dosage administration;

(viii) administration of single and multiple doses escalating from 5 mg/m^2/day via bolus;

(ix) oral dosages of below 30 mg/m^2;

(x) oral dosages of above 130 mg/m^2;

(xi) oral dosages up to 40 mg/m^2 for 3 days and then a nadir/recovery period of 18-21 days;

(xii) dosing at a lower level for an extended period;

(xiii) dosing at a higher level;

(xiv) dosing with a nadir/recovery period longer than 21 days;

(xv) the use of the substituted hexitol derivative as a single cytotoxic agent at 30 mg/m^2/day $\times$ 5 days, repeated monthly;

(xvi) dosing at 3 mg/kg;

(xvii) the use of a substituted hexitol derivative in combination therapy, at 30 mg/m^2/day $\times$ 5 days; and

(xviii) dosing at 40 mg/day $\times$ 5 days in adult patients, repeated every two weeks.

10. The method of claim 9 wherein the substiturted hexitol derivative is dianhydrogalactitol.

11. The method of claim 7 wherein the improvement is made by route of administration and the route of administration is at least one route of administration selected from the group consisting of:

(i) topical administration;

(ii) oral administration;

(iii) slow release oral delivery;

(iv) intrathecal administration;

(v) intraarterial administration;

(vi) continuous infusion;

(vii) intermittent infusion;

(viii) intravenous administration, such as intravenous administration for 30 minutes;

(ix) administration through a longer infusion; and

(x) administration through IV push.

12. The method of claim 10 wherein the substituted hexitol derivative is dianhydrogalactitol.

13. The method of claim 7 wherein the improvement is made by schedule of administration and the schedule of administration is at least one schedule of administration selected from the group consisting of:

(i) daily administration;

(ii) weekly administration;

(iii) weekly administration for three weeks;

(iv) biweekly administration;

(v) biweekly administration for three weeks with a 1-2 week rest period;

(vi) intermittent boost dose administration; and

(vii) daily administration for one week for multiple weeks.

14. The method of claim 13 wherein the substituted hexitol derivative is dianhydrogalactitol.

15. The method of claim 7 wherein the improvement is made by selection of disease stage and wherein the selection of disease stage is at least one selection of disease stage selected from the group consisting of:

(i) use in an appropriate disease stage for NSCLC;

(ii) use with an angiogenesis inhibitor to prevent or limit metastatic spread;

(iii) use for newly diagnosed disease;

(iv) use for recurrent disease; and

(v) use for resistant or refractory disease.

16. The method of claim 15 wherein the substituted hexitol derivative is dianhydrogalactitol.

17. The method of claim 7 wherein the improvement is made by patient selection and the patient selection is at least one patient selection carried out by a criterion selected from the group consisting of:

(i) selecting patients with a disease condition characterized by a high level of a metabolic enzyme selected from the group consisting of histone deacetylase and ornithine decarboxylase;

(ii) selecting patients with a low or high susceptibility to a condition selected from the group consisting of thrombocytopenia and neutropenia;

(iii) selecting patients intolerant of GI toxicities;

(iv) selecting patients characterized by over- or under-expression of a gene selected from the group consisting of c-Jun, a GPCR, a signal transduction protein, VEGF, a prostate-specific gene, and a protein kinase.

(v) selecting patients characterized by carrying extra copies of the EGFR gene for NSCLC;

(vi) selecting patients characterized by methylation or lack of methylation of the promoter of the MGMT gene;

(vii) selecting patients characterized by an unmethylated promoter region of MGMT (O^6-methylguanine methyltransferase);

(viii) selecting patients characterized by a methylated promoter region of MGMT;

(ix) selecting patients characterized by a high expression of MGMT;

(x) selecting patients characterized by a low expression of MGMT;

(xi) selecting patients characterized by a mutation in EGFR;

(xii) selecting patients being administered a platinum-based drug as combination therapy;

(xiii) selecting patients who do not have EGFR mutations and thus are less likely to respond to tyrosine kinase inhibitors (TKI);

(xiv) selecting patients who have become resistant to TKI treatment;

(xv) selecting patients who have the *BIM* co-deletion mutation and thus are less likely to respond to TKI treatment;

(xvi) selecting patients who have become resistant to platinum-based drug treatment; and

(xvii) selecting patients with brain metastases.

18. The method of claim 17 wherein the substituted hexitol derivative is dianhydrogalactitol.

19. The method of claim 17 wherein the criterion is selecting patients characterized by a mutation in EGFR and the mutation in EGFR is EGFR Variant III.

20. The method of claim 17 wherein the malignancy is NSCLC, and the patient selection is performed by detection or quantitation of a biomarker selected from the group consisting of:

(i) EGFR gene copy number;

(ii) the presence of an EGFR mutation selected from the group consisting of Exon 18 G719A; Exon 19 deletion; Exon 19 A743S; and Exon 21 L858R/L861Q;

(iii) EGFR protein expression;

(iv) p-Akt protein expression;

(v) the presence of *KRAS* mutations;

(vi) the presence of *BRAF* mutations;

(vii) mRNA levels for ERCC1;

(viii) DNA methylation;

(ix) low HER3;

(x) miRNA expression;

(xi) the presence of an allele selected from the group consisting of rs1051730 allele T, rs16969968 allele A, ss107794645 allele C, and rs8034191 allele C;

(xii) a marker selected from the group consisting of TOP1, TYMS, MGMT, PTEN, ERBB2, SPARC, ESR1, PGR, KIT, EGFR, PTGS2 and AR;

(xiii) arginine-rich metastasized in early tumors protein (ARMET);

(xiv) a CTAP-III related biomarker;

(xv) pErbB3;

(xvi) gene expression profiles;

(xvii) methylation state of nucleic acid encoding 14-3-3 sigma;

(xviii) a multigene signature;

(xix) phosphorylated Stat;

(xx) expression of survivin; and

(xxi) overexpression of a phosphorylated AKT protein and/or a phosphorylated MAPK protein.

21. The method of claim 17 wherein the malignancy is ovarian cancer, and the patient selection is performed by detection or quantitation of a biomarker selected from the group consisting of:

(i) a mutation in *BRCA1* or *BRCA2*;

(ii) hypermethylation of *BRCA1*, *RASSF1A*, *APC*, *p14ARF*, *p16INK4a*, or *DAPkinase*;

(iii) a gene expression profile specific for ovarian cancer;

(iv) a profile derived from serial analysis of gene expression (SAGE) for *CLDN3*, *HE4*, *FOLR1*, *COL18A1*, *CCND1*, or *FLJ12988*;

(v) a cleavage fragment of inter-α-trypsin inhibitor heavy chain H4;

(vi) transferrin;

(vii) afamin;

(viii) apoliprotein A-IV;

(ix) an miRNA expression profile;

(x) CA125 in serum;

(xi) DF3 in serum;

(xii) an alteration of a gene existing in a chromosomal region 2q14.2, 3p24.1, 3q26.2, 3q29, 4q34.2, 6q23, 9p21 3, 11q13.3, 13q22.1, 13q33.1, 13q33.3, 15q12, 15q15.1, 17p12, 17p13.1, 17p13.3, 18q21.1, 18q21.2, 18q21.31, 18q21.32, 18q21.33, 18q23, 20q13.13, 20q13.2, 20q13.31, 20q13.33, Xp11.23, Xp13.1, Xp13.3, Xp26.2, Xp26.3, or Xq28;

(xiii) modified ApoA1;

(xiv) a modified transthyretin selected from the group consisting of cysteinylated transthyretin, sulfonated transthyretin, CysGly modified transthyretin, and glutathionylated transthyretin;

(xv) a marker selected from the group consisting of CRP, EGF-R, CA-19-9, Apo-AI, Apo-CIII, IL-6, IL-18, MIP-1a, tenascin C and myoglobin and fragments thereof;

(xvi) methylation status of CpG dinucleotides;

(xvii) peptides derived from the degradation of CA125 present in urine;

(xviii) antibody for casein kinase 1;

(xix) a marker selected from the group consisting of calcyclin, calgranulin C, hepcidin, ApoC1, ApoAII, ApoCII, calgranulin A, and transthyretin;

(xx) elevated expression of *PVT1*;

(xxi) LIV-1;

(xxii) expression level of *MetAP2*;

(xxiii) a gene signature selected from the group consisting of 15-gene signature, a 23-gene signature, and a 28-gene signature;

(xxiv) a marker selected from the group consisting of p66-Shc and phosphorylated Shc;

(xxv) expression level of *S100A10* and *S100A11* as indicators of cisplatin resistance;

(xxvi) germline deletions of *BRCA1*;

(xxvii) epigenetic silencing of a gene selected from the group consisting of plasmolipin, TNFRSF10B tumor necrosis factor receptor superfamily (member 10b), RUNX3 runt-related transcription factor 3, ACTN1 actinin (alpha 1), and FANCG Fanconi anemia (complementation group G);

(xxviii) an elevated expression level of a gene involved in the O-glycan pathway, wherein the gene is selected from the group consisting of *B3GALT1*, *B3GALT2*, *B3GALT4*, *B3GALT5*, *B3GNT6*, *B4GALT1*, *B4GALT2*, *B4GALT3*, *C1GALT1*, *GALNT1*, *GALNT10*, *GALNT11*, *GALNT12*, *GALNT13*, *GALNT14*, *GALNT2*, *GALNT3*, *GALNT4*, *GALNT5*, *GALNT6*, *GALNT7*, *GALNT8*, *GALNT9*, *GALNTL1*, *GALNTL2*, *GALNTL4*, *GALNTL5*, *GCNT1*, *GCNT2*, *GCNT3*, *ST3GAL1*, *ST3GAL2*, *ST6GALN*, and *WBSCR17*;

(xxix) a marker selected from the group consisting of HE4, IL-2Rα, α-1-antitrypsin, YKL-40, cellular fibronectin, prostasin, TIMP-1, IL-8, VEGF-B, MMP-7, calprotectin, IGFBP-2, LOX-1, neuropilin-1, TNFR2, MPIF-1, and CA-72-4;

(xxx) a marker selected from the group consisting of CA 15-3 (MUC-1), Her2/Neu (erbB-2), kallikrein-5, Macrophage Inhibitory Factor (MIF), osteopontin, TAG-72, IGF-II, HE4, IL6-R, IL18-R, IL-18BP, VCAM-1, IP-10 (interferon-gamma inducible 10 kD protein), SMRP, TgII (tissue transglutaminase), exotaxin-1, Cyfra 21-1(cytokeratin 19 fragment), IGF2BP3, TIMP-1, alpha-1 antitrypsin, MMP7, IL-8, IL-6, sortillin, CD40, Alpha 1-Antichymotrypsin, VEGF, and haptoglobin; and

(xxxi) phosphorylation level of a BCL2 antagonist of cell death pathway protein, wherein the BCL2 antagonist of cell death pathway protein is BAD, Bax, BcL-XL, PP2C/PPM1A, AKT, EGFR, IRS-1, Shc, H-Ras, CDK1, G-protein alpha-s, G-protein beta/gamma, PI3K cat class 1A, c-Raf-1, p90Rsk, MEK2 (MAP2K2), PKA-cat, or PKA-reg.

22. The method of claim 5 wherein the improvement is made by analysis of patient or disease phenotype and the analysis of patient or disease

phenotype is a method of analysis of patient or disease phenotype carried out by a method selected from the group consisting of:

(a) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular phenotype;

(b) use of a method for measurement of a marker selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a protein that is a gene product of jun, and a protein kinase;

(c) surrogate compound dosing; and

(d) low dose pre-testing for enzymatic status.

23. The method of claim 22 wherein the substituted hexitol derivative is dianhydrogalactitol.

24. The method of claim 5 wherein the improvement is made by analysis of patient or disease genotype and wherein the method of analysis of patient or disease genotype is a method of analysis of patient or disease genotype carried out by a method selected from the group consisting of:

(i) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular genotype;

(ii) use of a gene chip;

(iii) use of gene expression analysis;

(iv) use of single nucleotide polymorphism (SNP) analysis;

(v) measurement of the level of a metabolite or a metabolic enzyme;

(vi) determination of copy number of the EGFR gene;

(vii) determination of status of methylation of promoter of MGMT gene;

(viii) determination of the existence of an unmethylated promoter region of the MGMT gene;

(ix) determination of the existence of a methylated promoter region of the MGMT gene;

(x) determination of the existence of high expression of MGMT;

(xi) determination of the existence of low expression of MGMT; and

(xii) for ovarian cancer, determination of the p53 genotype status.

25. The method of claim 24 wherein the method is use of single nucleotide polymorphism (SNP) analysis and wherein the SNP analysis is carried out on a gene selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a prostate specific gene, c-Jun, and a protein kinase.

26. The method of claim 24 wherein the substituted hexitol derivative is dianhydrogalactitol.

27. The method of claim 5 wherein the improvement is made by pre/post-treatment preparation and wherein the pre/post-treatment preparation is a method of pre/post treatment preparation selected from the group consisting of:

(i) the use of colchicine or an analog thereof;

(ii) the use of a diuretic;

(iii) the use of a uricosuric;

(iv) the use of uricase;

(v) the non-oral use of nicotinamide;

(vi) the use of a sustained-release form of nicotinamide;

(vii) the use of an inhibitor of poly-ADP ribose polymerase;

(viii) the use of caffeine;

(ix) the use of leucovorin rescue;

(x) infection control; and

(xi) the use of an anti-hypertensive agent.

28. The method of claim 27 wherein the substituted hexitol derivative is dianhydrogalactitol.

29. The method of claim 5 wherein the improvement is made by toxicity management and wherein the toxicity management is a method of toxicity management selected from the group consisting of:

(i) the use of colchicine or an analog thereof;

(ii) the use of a diuretic;

(iii) the use of a uricosuric;

(iv) the use of uricase;

(v) the non-oral use of nicotinamide;

(vi) the use of a sustained-release form of nicotinamide;

(vii) the use of an inhibitor of poly-ADP ribose polymerase;

(viii) the use of caffeine;

(ix) the use of leucovorin rescue;

(x) the use of sustained-release allopurinol;

(xi) the non-oral use of allopurinol;

(xii) the use of bone marrow transplants;

(xiii) the use of a blood cell stimulant;

(xiv) the use of blood or platelet infusions;

(xv) the administration of an agent selected from the group consisting of filgrastim, G-CSF, and GM-CSF;

(xvi) the application of a pain management technique;

(xvii) the administration of an anti-inflammatory agent;

(xviii) the administration of fluids;

(xix) the administration of a corticosteroid;

(xx) the administration of an insulin control medication;

(xxi) the administration of an antipyretic;

(xxii) the administration of an anti-nausea treatment;

(xxiii) the administration of an anti-diarrheal treatment;

(xxiv) the administration of N-acetylcysteine; and

(xxv) the administration of an antihistamine.

30. The method of claim 29 wherein the substituted hexitol derivative is dianhydrogalactitol.

31. The method of claim 5 wherein the improvement is made by pharmacokinetic/pharmacodynamic monitoring and wherein the pharmacokinetic/pharmacodynamic monitoring is a method selected from the group consisting of:

(i) multiple determinations of blood plasma levels; and

(ii) multiple determinations of at least one metabolite in blood or urine.

32. The method of claim 31 wherein the substituted hexitol derivative is dianhydrogalactitol.

33. The method of claim 5 wherein the improvement is made by drug combination and wherein the drug combination is a drug combination selected from the group consisting of:

(i) use with topoisomerase inhibitors;

(ii) use with fraudulent nucleosides;

(iii) use with fraudulent nucleotides;

(iv) use with thymidylate synthetase inhibitors;

(v) use with signal transduction inhibitors;

(vi) use with a platinum analog selected from the group consisting of cisplatin, oxaliplatin, and another chemotherapeutic platinum analog;

(vii) use with monofunctional alkylating agents;

(viii) use with bifunctional alkylating agents;

(ix) use with alkylating agents that damage DNA at a different place than does dianhydrogalactitol;

(x) use with anti-tubulin agents;

(xi) use with antimetabolites;

(xii) use with berberine;

(xiii) use with apigenin;

(xiv) use with amonafide;

(xv) use with colchicine or analogs;

(xvi) use with genistein;

(xvii) use with etoposide;

(xviii) use with cytarabine;

(xix) use with camptothecins

(xx) use with vinca alkaloids;

(xxi) use with 5-fluorouracil;

(xxii) use with curcumin;

(xxiii) use with NF-κB inhibitors;

(xxiv) use with rosmarinic acid;

(xxv) use with mitoguazone;

(xxvi) use with tetrandrine;

(xxvii) use with temozolomide;

(xxviii) use with VEGF inhibitors;

(xxix) use with cancer vaccines;

(xxx) use with EGFR inhibitors;

(xxxi) use with tyrosine kinase inhibitors;

(xxxii) use with poly (ADP-ribose) polymerase (PARP) inhibitors; and

(xxxiii) use with ALK inhibitors.

34. The method of claim 33 wherein the substituted hexitol derivative is dianhydrogalactitol.

35. The method of claim 5 wherein the method is for the treatment of NSCLC and wherein the drug combination is a drug combination selected from the group consisting of:

(i) use with 5-azacytidine;

(ii) use with a γ-secretase inhibitor;

(iii) use with a pyrroloquinolinyl-pyrrole-2,5-dione compound in combination with an EGFR inhibitor;

(iv) use with an inhibitor of the neurotensin activation of the neurotensin receptor 1 (NTSR1);

(v) use with a 14- or 15-membered-ring macrolide compound;

(vi) use with a water-soluble camptothecin analog;

(vii) use with 5-methyl-6-[[(3,4,5-trimethoxyphenyl)amino]-methyl]-2,4-quinazolinediamine (trimetrexate);

(viii) use with substituted pyrazolylpyridine, pyrazolylpyridazine, or pyrazolylpyrimidine derivatives;

(ix) use with hydrogen bond surrogate macrocyclic peptides;

(x) use with folate-vinca conjugates;

(xi) use with pyrazolopyrimidine PIK3 inhibitors;

(xii) use with 2-substituted-8-alkyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitriles;

(xiii) use with 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine bismesylate;

(xiv) use with morpholinylpurine derivatives;

(xv) use with a small molecule inhibitor of Replication Protein A that is a substituted haloester isoborneol;

(xvi) use with a tubulysin as an anti-mitotic agent;

(xvii) use with a quinazoline-based EGFR inhibitor containing a zinc binding moiety;

(xviii) use with substituted imidazo[1,2-a]pyrimidines or substituted imidazo[1,2-a]pyridines;

(xix) use with 7-*t*-butoxyiminomethylcamptothecin in combination with paclitaxel, epothilone B, cisplatin, carboplatin, {6-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-((R)-1-phenyl-ethyl)-amine, everolimus, imatinib, or bortezomib;

(xx) use with a sulfonylpyrrole as a HDAC inhibitor;

(xxi) use with 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide;

(xxii) use with aromatic bicyclic compounds with pyrimidine and pyridine moieties that are dual c-SRC/JAK inhibitors;

(xxiii) use with substituted 6,5-fused bicyclic heteroaryl compounds to prevent aberrant H3-K27 histone methylation;

(xxiv) use with substituted imidazopyridinyl-aminopyridine compounds;

(xxv) use with pyrimidine compounds as inhibitors of protein kinases IKKε and/or TBK-1;

(xxvi) use with unsaturated steroidal lactone derivatives related to bufadienolides;

(xxvii) use with the MEK inhibitor 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethyoxy)-amide and an antibody that is an IGFR1 inhibitor;

(xxviii) use with substituted amidopyridine or amidopyridazine derivatives that are histone demethylase inhibitors;

(xxix) use with phosphorus-substituted aryl compounds as ALK or c-Met kinase inhibitors;

(xxx) use with tetrahydrocarbazoles as VEGF synthesis inhibitors;

(xxxi) use with substituted heteroaryl- or aryl-cyclopropylamine acetamides as lysine specific demethylase-1 inhibitors;

(xxxii) use with rigidin analogs;

(xxxiii) use with 2-(2,4,5-substituted-anilino)pyrimidine compounds as inhibitors of mutated EGFR;

(xxxiv) use with alkylated piperazines as Btk inhibitors;

(xxxv) use with 3-[3-[[4-(dimethyloxidoaminomethy)anilino]-phenylmethylidene]-2-oxo-1H-indol-6-yl]-N-ethylprop-2-ynamide;

(xxxvi) use with quinazolines as serine/threonine kinase inhibitors;

(xxxvii) use with diazacarbazoles;

(xxxviii) use with modulators of K-Ras activity that include a Switch-2 binding pocket moiety and an electrophilic chemical moiety capable of forming a covalent bond with a K-Ras cysteine residue or a K-Ras aspartate residue;

(xxxix) use with inhibitors of mutants of isocitrate dehydrogenase 1 or isocitrate dehydrogenase 2;

(xl) use with hydroxamic acid derivatives that inhibit the HDAC pathway;

(xli) use with quinazoline derivatives as kinase inhibitors including one or more of EGFR, VEGFR-2, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFR, c-src, lck, Zap70 and fyn kinases;

(xlii) use with tricyclic PI3K inhibitors;

(xliii) use with furin inhibitors;

(xliv) use with sphingolipid analogs;

(xlv) use with niclosamide;

(xlvi) use with 3,5-disubstituted-3h-imidazo[4,5-b]pyridine or 3,5-disubstituted-3H-[1,2,3]triazolo[4,5-b]pyridine compounds as c-Met modulators;

(xlvii) use with 6-alkynylpyridine derivatives as SMAC mimetics;

(xlvii) use with naphthyridine derivatives;

(xlviii) use with bis-amidopyridines as SMAC mimetics;

(xlix) use with MEK inhibitors with imidazoquinolone or imidazoquinoline moieties;

(l) use with fused pyrimidine derivatives;

(li) use with imidazopyrazine, imidazopyridine, imidazopyridazine and imidazpyrimidine compounds or MNK1 or MNK2 inhibitors;

(lii) use with peptidomimetic macrocycles binding to MCL-1;

(liii) use with benzopyrazines as inhibitors of FGFR kinases;

(liv) use with fused bicyclic 2,4-diaminopyridine derivatives as dual ALK and FAK inhibitors;

(lv) use with boron-containing proteasome inhibitors;

(lvi) use with heteroaryl pyridone or aza-pyridone amide compounds as Btk inhibitors;

(lvii) use with substituted imidazopyrazines as PI3K/Akt inhibitors;

(lviii) use with derivatives of N-(arylamino) sulfonamides as MEK inhibitors;

(lix) use with sanguinarine;

(lx) use with beauvericin or analogs and derivatives thereof as Hsp90 chaperone pathway inhibitors;

(lxi) use with bis-(fluoroalkyl)-1,4-benzodiazapinone compounds as Notch receptor inhibitors;

(lxii) use with purinyl-containing heteroaryl compounds that inhibit DNA methyltransferase; and

(lxiii) use with antrocin.

36. The method of claim 5 wherein the method is for the treatment of ovarian cancer and wherein the drug combination is a drug combination selected from the group consisting of:

(i) use with paclitaxel;

(ii) use with docetaxel;

(iii) use with cisplatin;

(iv) use with carboplatin;

(v) use with topotecan;

(vi) use with gemcitabine

(vii) use with bleomycin;

(viii) use with etoposide;

(ix) use with doxorubicin;

(x) use with tamoxifen;

(xi) use with letrozole;

(xii) use with olaparib;

(xiii) use with selumetinib;

(xiv) use with mTOR inhibitors;

(xv) use with PI3 kinase inhibitors;

(xvi) use with trichostatin A;

(xvii) use with tricyclic compounds;

(xviii) use with piperidine/piperazine derivatives that are DGAT inhibitors;

(xix) use with pyrrolopyrimidine CHK1 or CHK2 inhibitors;

(xx) use with oxadiazole HDAC inhibitors;

(xxi) use with inhibitors of Replication Protein A that are haloester isoborneol derivatives;

(xxii) use with indazole inhibitors of TTK protein kinase;

(xxiii) use with combretastatin analogs;

(xxiv) use with HDAC inhibiting derivatives of camptothecin;

(xxv) use with piperazinylbenzamide PARP inhibitors;

(xxvi) use with BET bromodomain inhibitors;

(xxvii) use with platinum N-heterocyclic carbene derivatives;

(xxviii) use with NEDD8-activating enzyme inhibitors;

(xxix) use with cyclic peptidomimetic inhibitors of the WDR5/MLL1 interaction;

(xxx) use with anti-Ang-2 antibodies;

(xxxi) use with anti-TGFα antibodies;

(xxxii) use with NAMPT inhibitors;

(xxxiii) use with anti-α_2-integrin antibodies;

(xxxiv) use with 1,2,4-oxadiazole benzoic acid compounds;

(xxxv) use with tricylic pyrrole derivatives;

(xxxvi) use with anti-P-cadherin antibodies;

(xxxvii) use with BRAF kinase inhibitors;

(xxxviii) use with sulfonylpyrroles as HDAC inhibitors;

(xxxix) use with 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole;

(xl) use with triterpenoid derivatives;

(xli) use with chemokine CXCR4 modulators;

(xlii) use with 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide;

(xliii) use with CDK9 kinase inhibitors;

(xliv) use with substituted pyrimidinylpyrrolopyridinone derivatives;

(xlv) use with inhibitors of ATR kinase;

(xlvi) use with benzonitrile derivatives that are inhibitors of IKKε and TBK1;

(xlvii) use with DACT protein activators;

(xlviii) use with nitrogen mustard derivatives;

(xlix) use with alkoxychromenon-4-ones;

(l) use with pleckstrin homology domain inhibitors;

(li) use with 5-cyano-4-(pyrrolo [2,3-b] pyridine-3-yl)pyrimidine derivatives;

(lii) use with substituted aromatic bicyclic compounds as c-SRC/JAK inhibitors;

(liii) use with 7-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;

(liv) use with substituted 6,5-fused bicyclic aryl compounds;

(lv) use with substituted imidazopyridinyl-aminopyridine compounds;

(lvi) use with substituted imidazopyridines as HDM2 inhibitors;

(lvii) use with cycloalkylnitrile pyrazole carboxamides as janus kinase inhibitors;

(lviii) use with anti-ERBB3 antibodies;

(lvix) use with chroman derivatives;

(lx) use with 3-(indolyl)- and 3-(azaindolyl)-4-arylmaleimide compounds;

(lxi) use with c-Met inhibitors;

(lxii) use with pyrazolopyrimidines as ATR kinase inhibitors;

(lxiii) use with 3-pyrimidin-4-yl-oxazolidin-2-ones as inhibitors of mutant IDH;

(lxiv) use with migrastatin analogs;

(lxv) use with gemcitabine prodrugs;

(lxvi) use with substituted hydroxamic acids as HDAC6 inhibitors;

(lxvii) use with gonadotrophin-releasing hormone receptor antagonists;

(lxviii) use with inhibitors of anti-apoptotic Bcl-2 proteins;

(lxix) use with flavone derivatives that are inhibitors of MUC1 oligomerization;

(lxx) use with benzoxepin PI3K inhibitors;

(lxxi) use with tetrahydrouridine derivatives;

(lxxii) use with N-hydroxyamidino heterocycles as modulators of indoleamine 2,3-dioxygenase;

(lxxiii) use with heterocyclic apoptosis inhibitors;

(lxxiv) use with 3-aminocyclopentanecarboxamides as chemokine receptor antagonists;

(lxxv) use with polycyclic β-lactam derivatives;

(lxxvi) use with manassatin compounds that block the HIF pathway;

(lxxvii) use with heterocyclic carboxamides as AKT inhibitors;

(lxxvii) use with N,N′-bis(2-bromoethyl)phosphorodamidic acid (1-methyl-2-nitro-1H-imidazol-5-yl)methyl ester;

(lxxviii) use with substituted pyrrolo-, furano-, and cyclopentylpyrimidine bicyclic compounds;

(lxxix) use with 2-(2,4,5-substituted-anilino)pyrimidine compounds;

(lxxx) use with substituted [1,2,4]triazolo[4,3-a]pyrazines;

(lxxxi) use with indazole derivatives as ERK inhibitors;

(lxxxii) use with aryloxy phenoxy acrylic compounds;

(lxxxiii) use with pyrazolopyridine derivatives as NADPH oxidase inhibitors;

(lxxxiv) use with dihydronaphthyridines as c-Kit inhibitors;

(lxxxv) use with apoptosis-inducing agents;

(lxxxvi) use with unsymmetrical pyrrolobenzodiazepine dimers;

(lxxxvii) use with PRMT5 inhibitors;

(lxxxviii) use with apogossypolone derivatives;

(lxxxix) use with Hsp90 modulators;

(xc) use with pyridopyrazine compounds;

(xci) use with metastasis-reducing protease nexin 1 inhibitors;

(xcii) use with γ-secretase inhibitors;

(xciii) use with Axl inhibitors that are pyridone derivatives;

(xciv) use with (6R)-9-fluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(xcv) use with bridged bicyclic heteroaryl substituted triazoles as Axl inhibitors;

(xcvi) use with phosphoramidate derivatives of 5-fluoro-2′-deoxyuridine;

(xcvii) use with fused heterocyclic ring derivatives as Smo inhibitors;

(xcviii) use with thiochromeno[2,3-c]quinolin-12-one derivatives;

(xcix) use with quinazoline JAK inhibitors;

(c) use with di-2-pyridylketone 4-ethyl-4-methyl-3-thiosemicarbazone;

(ci) use with fused tricyclic inhibitors of mTOR;

(cii) use with 4-aza-2,3-didehydropodophyllotoxin compounds;

(ciii) use with triazole compounds that are Hsp90 inhibitors;

(civ) use with carbazole linked pyrrolo[2, 1-c][1,4]benzodiazepine hybrids as agents reacting with DNA to form an N2-guanine adduct that lies within the minor groove of duplex DNA via an acid-labile aminal bond to the electrophilic imine at the N10-C11 position;

(cv) use with lactam-substituted thio derivatives;

(cvi) use with pyridone amides as c-Met kinase inhibitors;

(cvii) use with benzothiazole derivatives selected from the group consisting of olefins, chalcones, pyrazolines, pyrazole, isoxazolines, and isoxazoles linked to 2-phenylbenzothiazoles;

(cviii) use with 7-(2-morpholin-4-yl-ethoxy)-2-(4-nitro-phenyl)imidazo[2,1-b][1,3]benzothiazole or 4-(7-(2-morpholinoethoxy)benzo[d]imidazo[2,1-b]thiazol-2-yl)aniline;

(cix) use with spiroketals;

(cx) use with pyrazole compounds as Hsp90 modulators;

(cxi) use with N-(4-(3-(2-aminopyrimidin-4-yl)pyridin-2-yloxy)phenyl)-4-(4-methylthiophen-2-yl)phthalazin-1-amine as Aurora kinase inhibitor;

(cxii) use with Axl ligand-binding portion of Axl tyrosine kinase receptor;

(cxiii) use with antibiotics as anti-angiogenesis agents;

(cxiv) use with a fatty acid binding protein inhibitor selected from the group consisting of carbazole butanoic acids, aryl sulfonamides, sulfonylthiophenes, 4-hydroxypyrimidines, 2,3-dimethylindoles, benzoylbenzenes, biphenyl-alkanoic acids, 2-oxazole-alkanoic acids, tetrahydropyrimidones, pyridones, pyrazinones, aryl carboxylic acids, tetrazoles, triazolopyrimidinones, indoles, BMS480404 ((2S)-2-[2,3-bis[(2-chlorophenyl)methoxy]phenyl]-2-hydroxyacetic acid), and BMS309403 (2-[[2'-(5-ethyl-3,4-diphenyl-1*H*-pyrazol-1-yl)[1,1'-biphenyl]-3-yl]oxy]-acetic acid;

(cxv) use with macitentan;

(cxvi) use with BRCA1 production enhancers;

(cxvii) use with farnesylthiosalicylic acid or analogs;

(cxviii) use with immunogenic peptides;

(cxix) use with interleukin 24 or interleukin 19;

(cxx) use with 2-phenyl-1-[4-(2-aminoethoxy)-benzyl]-indole derivatives;

(cxxi) use with karenitecin;

(cxxii) use with benzylidinebenzohydrazides;

(cxxiii) use with 5-[2-tert-butyl-5-(4-fluoro-phenyl)-1H-imidazol-4-yl]-3-(2,2-dimethyl-propyl)-3H-imidazo[4,5-b]pyridin-2-ylamine;

(cxxiv) use with 2-amino-4H-naphtho[1,2-b]pyran-3-carbonitriles;

(cxxv) use with Dll4 antagonists;

(cxxvi) use with prolactin receptor antagonist;

(cxxvii) use with cyclohexenone compounds;

(cxxviii) use with conjugates with CD56;

(cxxix) use with 17,20-lyase inhibitors;

(cxxx) use with angiopoietin-2 inhibitor;

(cxxxi) use with PARP inhibitors;

(cxxxii) use with water-soluble prodrugs;

(cxxxiii) use with a ginkgolide selected from the group consisting of ginkgolides A and B;

(cxxxiv) use with 4-(amino)-2(2,6-dioxo(3-piperidyl)-isoindoline-1,3-dione;

(cxxxv) use with antialamin; and

(cxxxvi) use with 1-glyoxylamide indolizines.

37. The method of claim 5 wherein the improvement is made by chemosensitization and the chemosensitization is the use of a substituted hexitol derivative as a chemosensitizer in combination with an agent selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;

(iii) fraudulent nucleotides;

(iv) thymidylate synthetase inhibitors;

(v) signal transduction inhibitors;

(vi) a platinum analog selected from the group consisting of cisplatin, oxaliplatin, and another platinum analog;

(vii) alkylating agents;

(viii) anti-tubulin agents;

(ix) antimetabolites;

(x) berberine;

(xi) apigenin;

(xii) amonafide;

(xiii) colchicine or analogs;

(xiv) genistein;

(xv) etoposide;

(xvi) cytarabine;

(xvii) camptothecins;

(xviii) vinca alkaloids;

(xix) topoisomerase inhibitors;

(xx) 5-fluorouracil;

(xxi) curcumin;

(xxii) NF-κB inhibitors;

(xxiii) rosmarinic acid;

(xxiv) mitoguazone;

(xxv) tetrandrine;

(xxvi) a tyrosine kinase inhibitor;

(xxvii) an inhibitor of EGFR; and

(xxviii) an inhibitor of PARP.

38. The method of claim 37 wherein the substituted hexitol derivative is dianhydrogalactitol.

39. The method of claim 5 wherein the improvement is made by chemopotentiation and the chemosensitization is the use of a substituted hexitol derivative as a chemopotentiator in combination with an agent selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;

(iii) fraudulent nucleotides;

(iv) thymidylate synthetase inhibitors;

(v) signal transduction inhibitors;

(vi) a platinum analog selected from the group consisting of cisplatin, oxaliplatin, and another platinum analog;

(vii) alkylating agents;

(viii) anti-tubulin agents;

(ix) antimetabolites;

(x) berberine;

(xi) apigenin;

(xii) amonafide;

(xiii) colchicine or analogs;

(xiv) genistein;

(xv) etoposide;

(xvi) cytarabine;

(xvii) camptothecins;

(xviii) vinca alkaloids;

(xix) 5-fluorouracil;

(xx) curcumin;

(xxi) NF-κB inhibitors;

(xxii) rosmarinic acid;

(xxiii) mitoguazone;

(xxiv) tetrandrine;

(xxv) a tyrosine kinase inhibitor;

(xxvi) an inhibitor of EGFR; and

(xxvii) an inhibitor of PARP.

40. The method of claim 39 wherein the substituted hexitol derivative is dianhydrogalactitol.

41. The method of claim 5 wherein the improvement is made by by post-treatment management and the post-treatment management is a method selected from the group consisting of:

(i) a therapy associated with pain management;

(ii) administration of an anti-emetic;

(iii) an anti-nausea therapy;

(iv) administration of an anti-inflammatory agent;

(v) administration of an anti-pyretic agent; and

(vi) administration of an immune stimulant.

42. The method of claim 41 wherein the substituted hexitol derivative is dianhydrogalactitol.

43. The method of claim 5 wherein the improvement is made by alternative medicine/post-treatment support and the alternative medicine/post-treatment support is a method selected from the group consisting of:

(i) hypnosis;

(ii) acupuncture;

(iii) meditation;

(iv) a herbal medication created either synthetically or through extraction; and

(v) applied kinesiology.

44. The method of claim 43 wherein the substituted hexitol derivative is dianhydrogalactitol.

45. The method of claim 5 wherein the improvement is made by a bulk drug product improvement and the bulk drug product improvement is a bulk drug product improvement selected from the group consisting of:

(i) salt formation;

(ii) preparation as a homogeneous crystal structure;

(iii) preparation as a pure isomer;

(iv) increased purity;

(v) preparation with lower residual solvent content; and

(vi) preparation with lower residual heavy metal content.

46. The method of claim 45 wherein the substituted hexitol derivative is dianhydrogalactitol.

47. The method of claim 5 wherein the improvement is made by use of a diluent and the diluent is a diluent selected from the group consisting of:

(i) an emulsion;

(ii) dimethylsulfoxide (DMSO);

(iii) N-methylformamide (NMF)

(iv) DMF;

(v) ethanol;

(vi) benzyl alcohol;

(vii) dextrose-containing water for injection;

(viii) Cremophor;

(ix) cyclodextrin; and

(x) PEG.

48. The method of claim 47 wherein the substituted hexitol derivative is dianhydrogalactitol.

49. The method of claim 5 wherein the improvement is made by use of a solvent system and the solvent system is a solvent system selected from the group consisting of:

(i) an emulsion;

(ii) dimethylsulfoxide (DMSO);

(iii) N-methylformamide (NMF)

(iv) DMF;

(v) ethanol;

(vi) benzyl alcohol;

(vii) dextrose-containing water for injection;

(viii) Cremophor;

(ix) cyclodextrin; and

(x) PEG.

50. The method of claim 49 wherein the substituted hexitol derivative is dianhydrogalactitol.

51. The method of claim 5 wherein the improvement is made by use of an excipient and the excipient is an excipient selected from the group consisting of:

(i) mannitol;

(ii) albumin;

(iii) EDTA;

(iv) sodium bisulfite;

(v) benzyl alcohol;

(vi) a carbonate buffer; and

(vii) a phosphate buffer.

52. The method of claim 51 wherein the substituted hexitol derivative is dianhydrogalactitol.

53. The method of claim 5 wherein the improvement is made by use of a dosage form and the dosage form is a dosage form selected from the group consisting of:

(i) tablets;

(ii) capsules;

(iii) topical gels;

(iv) topical creams;

(v) patches;

(vi) suppositories; and

(vii) lyophilized dosage fills.

54. The method of claim 53 wherein the substituted hexitol derivative is dianhydrogalactitol.

55. The method of claim 5 wherein the improvement is made by use of dosage kits and packaging and the dosage kits and packaging are selected from the group consisting of the use of amber vials to protect from light and the use of stoppers with specialized coatings to improve shelf-life stability.

56. The method of claim 55 wherein the substituted hexitol derivative is dianhydrogalactitol.

57. The method of claim 5 wherein the improvement is made by use of a drug delivery system and the drug delivery system is a drug delivery system selected from the group consisting of:

(i) nanocrystals;

(ii) bioerodible polymers;

(iii) liposomes;

(iv) slow release injectable gels; and

(v) microspheres.

58. The method of claim 57 wherein the substituted hexitol derivative is dianhydrogalactitol.

59. The method of claim 5 wherein the improvement is made by use of a drug conjugate form and the drug conjugate form is selected from the group consisting of:

(i) a polymer system;

(ii) polylactides;

(iii) polyglycolides;

(iv) amino acids;

(v) peptides; and

(vi) multivalent linkers.

60. The method of claim 53 wherein the substituted hexitol derivative is dianhydrogalactitol.

61. The method of claim 5 wherein the therapeutic agent is a modified substituted hexitol derivative that is a compound analog and the modification is selected from the group consisting of:

(i) alteration of side chains to increase or decrease lipophilicity;

(ii) addition of an additional chemical functionality to alter a property selected from the group consisting of reactivity, electron affinity, and binding capacity; and

(iii) alteration of salt form.

62. The method of claim 55 wherein the modified substituted hexitol derivative is a compound analog of dianhydrogalactitol.

63. The method of claim 5 wherein the substituted hexitol derivative is in the form of a prodrug system and wherein the prodrug system is a prodrug system selected from the group consisting of:

(i) the use of enzyme sensitive esters;

(ii) the use of dimers;

(iii) the use of Schiff bases;

(iv) the use of pyridoxal complexes; and

(v) the use of caffeine complexes.

64. The method of claim 63 wherein the prodrug system is a prodrug system comprising a prodrug of dianhydrogalactitol.

65. The method of claim 5 wherein the improvement is made by use of a multiple drug system and the multiple drug system is a multiple drug system selected from the group consisting of:

(i) use of multi-drug resistance inhibitors;

(ii) use of specific drug resistance inhibitors;

(iii) use of specific inhibitors of selective enzymes;

(iv) use of signal transduction inhibitors;

(v) use of repair inhibition; and

(vi) use of topoisomerase inhibitors with non-overlapping side effects.

66. The method of claim 65 wherein the substituted hexitol derivative is dianhydrogalactitol.

67. The method of claim 5 wherein the improvement is made by biotherapeutic enhancement and the biotherapeutic enhancement is performed by use in combination as sensitizers/potentiators with a therapeutic agent or technique that is a therapeutic agent or technique selected from the group consisting of:

(i) cytokines;
(ii) lymphokines;
(iii) therapeutic antibodies;
(iv) antisense therapies;
(v) gene therapies;
(vi) ribozymes;
(vii) RNA interference; and
(viii) vaccines.

68. The method of claim 67 wherein the substituted hexitol derivative is dianhydrogalactitol.

69. The method of claim 5 wherein the improvement is made by biotherapeutic resistance modulation and the biotherapeutic resistance modulation is use against NSCLC resistant to a therapeutic agent or technique selected from the group consisting of:

(i) biological response modifiers;
(ii) cytokines;
(iii) lymphokines;
(iv) therapeutic antibodies;
(v) antisense therapies;
(vi) gene therapies;
(vii) ribozymes;
(viii) RNA interference; and
(ix) vaccines.

70. The method of claim 69 wherein the substituted hexitol derivative is dianhydrogalactitol.

71. The method of claim 5 wherein the improvement is made by radiation therapy enhancement and the radiation therapy enhancement is a radiation therapy enhancement agent or technique selected from the group consisting of:

(i) hypoxic cell sensitizers;

(ii) radiation sensitizers/protectors;

(iii) photosensitizers;

(iv) radiation repair inhibitors;

(e) thiol depleters;

(f) vaso-targeted agents;

(g) DNA repair inhibitors;

(h) radioactive seeds;

(i) radionuclides;

(j) radiolabeled antibodies; and

(k) brachytherapy.

72. The method of claim 71 wherein the substituted hexitol is dianhydrogalactitol.

73. The method of claim 5 wherein the improvement is made by use of a novel mechanism of action and the novel mechanism of action is a therapeutic interaction with a target or mechanism selected from the group consisting of:

(i) inhibitors of poly-ADP ribose polymerase;

(ii) agents that affect vasculature or vasodilation;

(iii) oncogenic targeted agents;

(iv) signal transduction inhibitors;

(v) EGFR inhibition;

(vi) protein kinase C inhibition;

(vii) phospholipase C downregulation;

(viii) Jun downregulation;

(ix) histone genes;

(x) VEGF;

(xi) ornithine decarboxylase;

(xii) ubiquitin C;

(xiii) Jun D;

(xiv) v-Jun;

(xv) GPCRs;

(xvi) protein kinase A;

(xvii) protein kinases other than protein kinase A;

(xviii) prostate specific genes;

(xix) telomerase;

(xx) histone deacetylase; and

(xxi) tyrosine kinase inhibitors.

74. The method of claim 73 wherein the substituted hexitol derivative is dianhydrogalactitol.

75. The method of claim 5 wherein the improvement is made by use of selective target cell population therapeutics and the use of selective target cell population therapeutics is a use selected from the group consisting of:

(i) use against radiation sensitive cells;

(ii) use against radiation resistant cells; and

(iii) use against energy depleted cells.

76. The method of claim 75 wherein the substituted hexitol derivative is dianhydrogalactitol.

77. The method of claim 5 wherein the improvement is made by use of a substituted hexitol derivative in combination with ionizing radiation.

78. The method of claim 77 wherein the substituted hexitol derivative is dianhydrogalactitol.

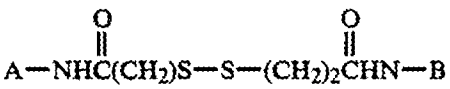
79. The method of claim 5 wherein the improvement is made by use of an agent that counteracts myelosuppression and the agent that counteracts myelosuppression is a dithiocarbamate.

80. The method of claim 79 wherein the substituted hexitol derivative is dianhydrogalactitol.

81. The method of claim 5 wherein the improvement is made by use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier to treat brain metastases of NSCLC and the agent that increases the

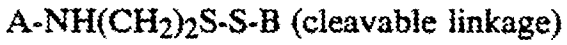
ability of the substituted hexitol to pass through the blood-brain barrier is an agent selected from the group consisting of:

(i) a chimeric peptide of the structure of Formula (D-III):



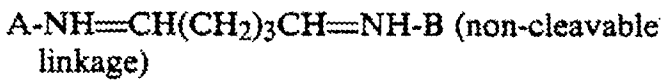
(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):



(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):



(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

(ii) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(iii) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(iv) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(v) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

82. The method of claim 81 wherein the substituted hexitol derivative is dianhydrogalactitol.

83. A composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing a substituted hexitol derivative for the treatment of a malignancy selected from the group consisting of NSCLC and ovarian cancer comprising an alternative selected from the group consisting of:

(a) a therapeutically effective quantity of a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative, wherein the modified substituted hexitol derivative or the derivative, analog or prodrug of the substituted hexitol derivative or modified substituted hexitol derivative possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative;

(b) a composition comprising:

(i) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative, or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative; and

(ii) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, drug delivery system, agent to counteract myelosuppression, or agent that increases the ability of the substituted hexitol to pass through the blood-

brain barrier, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative;

(c) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is incorporated into a dosage form, wherein the substituted hexitol derivative, the modified substituted hexitol derivative or the derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative;

(d) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is incorporated into a dosage kit and packaging, wherein the substituted hexitol derivative, the modified substituted hexitol derivative or the derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative incorporated into the dosage kit and packaging possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative; and

(e) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is subjected to a bulk drug product improvement, wherein substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative subjected to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or ovarian cancer as compared with an unmodified substituted hexitol derivative.

84. The composition of claim 83 wherein the composition improves the efficacy and/or reduces the side effects of suboptimally administered drug therapy employing a substituted hexitol derivative for the treatment of NSCLC.

85. The composition of claim 83 wherein the composition improves the efficacy and/or reduces the side effects of suboptimally administered drug therapy employing a substituted hexitol derivative for the treatment of ovarian cancer.

86. The composition of claim 83 wherein the unmodified substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol.

87. The composition of claim 86 wherein the unmodified substituted hexitol derivative is dianhydrogalactitol.

88. The composition of claim 83 wherein the composition comprises a drug combination comprising:

(a) a substituted hexitol derivative; and

(b) an additional therapeutic agent selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;

(iii) fraudulent nucleotides;

(iv) thymidylate synthetase inhibitors;

(v) signal transduction inhibitors;

(vi) a platinum analog selected from the group consisting of cisplatin, oxaliplatin, and another platinum analog;

(vii) monofunctional alkylating agents;

(viii) bifunctional alkylating agents;

(ix) alkylating agents that damage DNA at a different place than does dianhydrogalactitol;

(x) anti-tubulin agents;

(xi) antimetabolites;

(xii) berberine;

(xiii) apigenin;

(xiv) amonafide;

(xv) colchicine or analogs;

(xvi) genistein;

(xvii) etoposide;

(xviii) cytarabine;

(xix) camptothecins;

(xx) vinca alkaloids;

(xxi) 5-fluorouracil;

(xxii) curcumin;

(xxiii) NF-κB inhibitors;

(xxiv) rosmarinic acid;

(xxv) mitoguazone;

(xxvi) tetrandrine;

(xxvii) temozolomide;

(xxviii) VEGF inhibitors;

(xxix) cancer vaccines;

(xxx) EGFR inhibitors;

(xxxi) tyrosine kinase inhibitors; and

(xxxii) poly (ADP-ribose) polymerase (PARP) inhibitors.

89. The composition of claim 88 wherein the substituted hexitol derivative is dianhydrogalactitol.

90. The composition of claim 83 wherein the composition is formulated for treatment of NSCLC and comprises a drug combination comprising:

(a) a substituted hexitol derivative; and

(b) an additional therapeutic agent selected from the group consisting of:

(i) 5-azacytidine;

(ii) a γ-secretase inhibitor;

(iii) a pyrroloquinolinyl-pyrrole-2,5-dione compound in combination with an EGFR inhibitor;

(iv) an inhibitor of the neurotensin activation of the neurotensin receptor 1 (NTSR1);

(v) a 14- or 15-membered-ring macrolide compound;

(vi) a water-soluble camptothecin analog;

(vii) 5-methyl-6-[[(3,4,5-trimethoxyphenyl)amino]-methyl]-2,4-quinazolinediamine (trimetrexate);

(viii) substituted pyrazolylpyridine, pyrazolylpyridazine, or pyrazolylpyrimidine derivatives;

(ix) hydrogen bond surrogate macrocyclic peptides;

(x) folate-vinca conjugates;

(xi) pyrazolopyrimidine PIK3 inhibitors;

(xii) 2-substituted-8-alkyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitriles;

(xiii) 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine bismesylate;

(xiv) morpholinylpurine derivatives;

(xv) a small molecule inhibitor of Replication Protein A that is a substituted haloester isoborneol;

(xvi) a tubulysin as an anti-mitotic agent;

(xvii) a quinazoline-based EGFR inhibitor containing a zinc binding moiety;

(xviii) substituted imidazo[1,2-a]pyrimidines or substituted imidazo[1,2-a]pyridines;

(xix) 7-*t*-butoxyiminomethylcamptothecin in combination with paclitaxel, epothilone B, cisplatin, carboplatin, {6-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-((R)-1-phenyl-ethyl)-amine, everolimus, imatinib, or bortezomib;

(xx) a sulfonylpyrrole as a HDAC inhibitor;

(xxi) 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide;

(xxii) aromatic bicyclic compounds with pyrimidine and pyridine moieties that are dual c-SRC/JAK inhibitors;

(xxiii) substituted 6,5-fused bicyclic heteroaryl compounds to prevent aberrant H3-K27 histone methylation;

(xxiv) substituted imidazopyridinyl-aminopyridine compounds;

(xxv) pyrimidine compounds as inhibitors of protein kinases IKKε and/or TBK-1;

(xxvi) unsaturated steroidal lactone derivatives related to bufadienolides;

(xxvii) the MEK inhibitor 6-(4-bromo-2-fluorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethyoxy)-amide and an antibody that is an IGFR1 inhibitor;

(xxviii) substituted amidopyridine or amidopyridazine derivatives that are histone demethylase inhibitors;

(xxix) phosphorus-substituted aryl compounds as ALK or c-Met kinase inhibitors;

(xxx) tetrahydrocarbazoles as VEGF synthesis inhibitors;

(xxxi) substituted heteroaryl- or aryl-cyclopropylamine acetamides as lysine specific demethylase-1 inhibitors;

(xxxii) rigidin analogs;

(xxxiii) 2-(2,4,5-substituted-anilino)pyrimidine compounds as inhibitors of mutated EGFR;

(xxxiv) alkylated piperazines as Btk inhibitors;

(xxxv) 3-[3-[[4-(dimethyloxidoaminomethy)anilino]-phenylmethylidene]-2-oxo-1H-indol-6-yl]-N-ethylprop-2-ynamide;

(xxxvi) quinazolines as serine/threonine kinase inhibitors;

(xxxvii) diazacarbazoles;

(xxxviii) modulators of K-Ras activity that include a Switch-2 binding pocket moiety and an electrophilic chemical moiety capable of forming a covalent bond with a K-Ras cysteine residue or a K-Ras aspartate residue;

(xxxix) inhibitors of mutants of isocitrate dehydrogenase 1 or isocitrate dehydrogenase 2;

(xl) hydroxamic acid derivatives that inhibit the HDAC pathway;

(xli) quinazoline derivatives as kinase inhibitors including one or more of EGFR, VEGFR-2, c-erbB-2, c-erbB-4, c-met, tie-2, PDGFR, c-src, lck, Zap70 and fyn kinases;

(xlii) tricyclic PI3K inhibitors;

(xliii) furin inhibitors;

(xliv) sphingolipid analogs;

(xlv) niclosamide;

(xlvi) 3,5-disubstituted-3h-imidazo[4,5-b]pyridine or 3,5-disubstituted-3H-[1,2,3]triazolo[4,5-b]pyridine compounds as c-Met modulators;

(xlvii) 6-alkynylpyridine derivatives as SMAC mimetics;

(xlvii) naphthyridine derivatives;

(xlviii) bis-amidopyridines as SMAC mimetics;

(xlix) MEK inhibitors with imidazoquinolone or imidazoquinoline moieties;

(l) fused pyrimidine derivatives;

(li) imidazopyrazine, imidazopyridine, imidazopyridazine and imidazpyrimidine compounds or MNK1 or MNK2 inhibitors;

(lii) peptidomimetic macrocycles binding to MCL-1;

(liii) benzopyrazines as inhibitors of FGFR kinases;

(liv) fused bicyclic 2,4-diaminopyridine derivatives as dual ALK and FAK inhibitors;

(lv) boron-containing proteasome inhibitors;

(lvi) heteroaryl pyridone or aza-pyridone amide compounds as Btk inhibitors;

(lvii) substituted imidazopyrazines as PI3K/Akt inhibitors;

(lviii) derivatives of N-(arylamino) sulfonamides as MEK inhibitors;

(lix) sanguinarine;

(lx) beauvericin or analogs and derivatives thereof as Hsp90 chaperone pathway inhibitors;

(lxi) bis-(fluoroalkyl)-1,4-benzodiazapinone compounds as Notch receptor inhibitors;

(lxii) purinyl-containing heteroaryl compounds that inhibit DNA methyltransferase; and

(lxiii) antrocin.

91. The composition of claim 83 wherein the composition is formulated for treatment of ovarian cancer and comprises a drug combination comprising:

(a) a substituted hexitol derivative; and

(b) an additional therapeutic agent selected from the group consisting of:

(i) paclitaxel;

(ii) docetaxel;

(iii) cisplatin;

(iv) carboplatin;

(v) topotecan;

(vi) gemcitabine

(vii) bleomycin;

(viii) etoposide;

(ix) doxorubicin;

(x) tamoxifen;

(xi) letrozole;

(xii) olaparib;

(xiii) selumetinib;

(xiv) mTOR inhibitors;

(xv) PI3 kinase inhibitors;

(xvi) trichostatin A;

(xvii) tricyclic compounds;

(xviii) piperidine/piperazine derivatives that are DGAT inhibitors;

(xix) pyrrolopyrimidine CHK1 or CHK2 inhibitors;

(xx) oxadiazole HDAC inhibitors;

(xxi) inhibitors of Replication Protein A that are haloester isoborneol derivatives;

(xxii) indazole inhibitors of TTK protein kinase;

(xxiii) combretastatin analogs;

(xxiv) HDAC inhibiting derivatives of camptothecin;

(xxv) piperazinylbenzamide PARP inhibitors;

(xxvi) BET bromodomain inhibitors;

(xxvii) platinum N-heterocyclic carbene derivatives;

(xxviii) NEDD8-activating enzyme inhibitors;

(xxix) cyclic peptidomimetic inhibitors of the WDR5/MLL1 interaction;

(xxx) anti-Ang-2 antibodies;

(xxxi) anti-TGFα antibodies;

(xxxii) NAMPT inhibitors;

(xxxiii) anti-α_2-integrin antibodies;

(xxxiv) 1,2,4-oxadiazole benzoic acid compounds;

(xxxv) tricylic pyrrole derivatives;

(xxxvi) anti-P-cadherin antibodies;

(xxxvii) BRAF kinase inhibitors;

(xxxviii) sulfonylpyrroles as HDAC inhibitors;

(xxxix) 3-(2,4-dihydroxy-5-isopropyl-phenyl)-4-(1-methyl-indol-5-yl)-5-hydroxy-[1,2,4]triazole;

(xl) triterpenoid derivatives;

(xli) chemokine CXCR4 modulators;

(xlii) 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide;

(xliii) CDK9 kinase inhibitors;

(xliv) substituted pyrimidinylpyrrolopyridinone derivatives;

(xlv) inhibitors of ATR kinase;

(xlvi) benzonitrile derivatives that are inhibitors of IKKε and TBK1;

(xlvii) DACT protein activators;

(xlviii) nitrogen mustard derivatives;

(xlix) alkoxychromenon-4-ones;

(l) pleckstrin homology domain inhibitors;

(li) 5-cyano-4-(pyrrolo [2,3-b] pyridine-3-yl)pyrimidine derivatives;

(lii) substituted aromatic bicyclic compounds as c-SRC/JAK inhibitors;

(liii) 7-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide;

(liv) substituted 6,5-fused bicyclic aryl compounds;

(lv) substituted imidazopyridinyl-aminopyridine compounds;

(lvi) substituted imidazopyridines as HDM2 inhibitors;

(lvii) cycloalkylnitrile pyrazole carboxamides as janus kinase inhibitors;

(lviii) anti-ERBB3 antibodies;

(lvix) chroman derivatives;

(lx) 3-(indolyl)- and 3-(azaindolyl)-4-arylmaleimide compounds;

(lxi) c-Met inhibitors;

(lxii) pyrazolopyrimidines as ATR kinase inhibitors;

(lxiii) 3-pyrimidin-4-yl-oxazolidin-2-ones as inhibitors of mutant IDH;

(lxiv) migrastatin analogs;

(lxv) gemcitabine prodrugs;

(lxvi) substituted hydroxamic acids as HDAC6 inhibitors;

(lxvii) gonadotrophin-releasing hormone receptor antagonists;

(lxviii) inhibitors of anti-apoptotic Bcl-2 proteins;

(lxix) flavone derivatives that are inhibitors of MUC1 oligomerization;

(lxx) benzoxepin PI3K inhibitors;

(lxxi) tetrahydrouridine derivatives;

(lxxii) N-hydroxyamidino heterocycles as modulators of indoleamine 2,3-dioxygenase;

(lxxiii) heterocyclic apoptosis inhibitors;

(lxxiv) 3-aminocyclopentanecarboxamides as chemokine receptor antagonists;

(lxxv) polycyclic β-lactam derivatives;

(lxxvi) manassatin compounds that block the HIF pathway;

(lxxvii) heterocyclic carboxamides as AKT inhibitors;

(lxxvii) N,N′-bis(2-bromoethyl)phosphorodamidic acid (1-methyl-2-nitro-1H-imidazol-5-yl)methyl ester;

(lxxviii) substituted pyrrolo-, furano-, and cyclopentylpyrimidine bicyclic compounds;

(lxxix) 2-(2,4,5-substituted-anilino)pyrimidine compounds;

(lxxx) substituted [1,2,4]triazolo[4,3-a]pyrazines;

(lxxxi) indazole derivatives as ERK inhibitors;

(lxxxii) aryloxy phenoxy acrylic compounds;

(lxxxiii) pyrazolopyridine derivatives as NADPH oxidase inhibitors;

(lxxxiv) dihydronaphthyridines as c-Kit inhibitors;

(lxxxv) apoptosis-inducing agents;

(lxxxvi) unsymmetrical pyrrolobenzodiazepine dimers;

(lxxxvii) PRMT5 inhibitors;

(lxxxviii) apogossypolone derivatives;

(lxxxix) Hsp90 modulators;

(xc) pyridopyrazine compounds;

(xci) metastasis-reducing protease nexin 1 inhibitors;

(xcii) γ-secretase inhibitors;

(xciii) Axl inhibitors that are pyridone derivatives;

(xciv) (6R)-9-fluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(xcv) bridged bicyclic heteroaryl substituted triazoles as Axl inhibitors;

(xcvi) phosphoramidate derivatives of 5-fluoro-2′-deoxyuridine;

(xcvii) fused heterocyclic ring derivatives as Smo inhibitors;

(xcviii) thiochromeno[2,3-c]quinolin-12-one derivatives;

(xcix) quinazoline JAK inhibitors;

(c) di-2-pyridylketone 4-ethyl-4-methyl-3-thiosemicarbazone;

(ci) fused tricyclic inhibitors of mTOR;

(cii) 4-aza-2,3-didehydropodophyllotoxin compounds;

(ciii) triazole compounds that are Hsp90 inhibitors;

(civ) carbazole linked pyrrolo[2, 1-c][1,4]benzodiazepine hybrids as agents reacting with DNA to form an N2-guanine adduct that lies within the minor groove of duplex DNA via an acid-labile aminal bond to the electrophilic imine at the N10-C11 position;

(cv) lactam-substituted thio derivatives;

(cvi) pyridone amides as c-Met kinase inhibitors;

(cvii) benzothiazole derivatives selected from the group consisting of olefins, chalcones, pyrazolines, pyrazole, isoxazolines, and isoxazoles linked to 2-phenylbenzothiazoles;

(cviii) 7-(2-morpholin-4-yl-ethoxy)-2-(4-nitro-phenyl)imidazo[2,1-b][1,3]benzothiazole or 4-(7-(2-morpholinoethoxy)benzo[d]imidazo[2,1-b]thiazol-2-yl)aniline;

(cix) spiroketals;

(cx) pyrazole compounds as Hsp90 modulators;

(cxi) N-(4-(3-(2-aminopyrimidin-4-yl)pyridin-2-yloxy)phenyl)-4-(4-methylthiophen-2-yl)phthalazin-1-amine as Aurora kinase inhibitor;

(cxii) Axl ligand-binding portion of Axl tyrosine kinase receptor;

(cxiii) antibiotics as anti-angiogenesis agents;

(cxiv) a fatty acid binding protein inhibitor selected from the group consisting of carbazole butanoic acids, aryl sulfonamides, sulfonylthiophenes, 4-hydroxypyrimidines, 2,3-dimethylindoles, benzoylbenzenes, biphenyl-alkanoic acids, 2-oxazole-alkanoic acids, tetrahydropyrimidones, pyridones, pyrazinones, aryl carboxylic acids, tetrazoles, triazolopyrimidinones, indoles, BMS480404 ((2S)-2-[2,3-bis[(2-chlorophenyl)methoxy]phenyl]-2-hydroxyacetic acid), and BMS309403 (2-[[2'-(5-ethyl-3,4-diphenyl-1*H*-pyrazol-1-yl)[1,1'-biphenyl]-3-yl]oxy]-acetic acid;

(cxv) macitentan;

(cxvi) BRCA1 production enhancers;

(cxvii) farnesylthiosalicylic acid or analogs;

(cxviii) immunogenic peptides;

(cxix) interleukin 24 or interleukin 19;

(cxx) 2-phenyl-1-[4-(2-aminoethoxy)-benzyl]-indole derivatives;

(cxxi) karenitecin;

(cxxii) benzylidinebenzohydrazides;

(cxxiii) 5-[2-tert-butyl-5-(4-fluoro-phenyl)-1H-imidazol-4-yl]-3-(2,2-dimethyl-propyl)-3H-imidazo[4,5-b]pyridin-2-ylamine;

(cxxiv) 2-amino-4H-naphtho[1,2-b]pyran-3-carbonitriles;

(cxxv) Dll4 antagonists;

(cxxvi) prolactin receptor antagonist;

(cxxvii) cyclohexenone compounds;

(cxxviii) conjugates with CD56;

(cxxix) 17,20-lyase inhibitors;

(cxxx) angiopoietin-2 inhibitor;

(cxxxi) PARP inhibitors;

(cxxxii) water-soluble prodrugs;

(cxxxiii) a ginkgolide selected from the group consisting of ginkgolides A and B;

(cxxxiv) 4-(amino)-2(2,6-dioxo(3-piperidyl)-isoindoline-1,3-dione;

(cxxxv) antialamin; and

(cxxxvi) 1-glyoxylamide indolizines.

92. The composition of claim 83 wherein the composition comprises:

(a) a substituted hexitol derivative; and

(b) a therapeutic agent subject to chemosensitization selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;

(iii) fraudulent nucleotides;

(iv) thymidylate synthetase inhibitors;

(v) signal transduction inhibitors;

(vi) a platinum analog selected from the group consisting of cisplatin, oxaliplatin, and another platinum analog;

(vii) alkylating agents;

(viii) anti-tubulin agents;

(ix) antimetabolites;

(x) berberine;

(xi) apigenin;

(xii) amonafide;

(xiii) colchicine or analogs;

(xiv) genistein;

(xv) etoposide;

(xvi) cytarabine;

(xvii) camptothecins;

(xviii) vinca alkaloids;

(xix) topoisomerase inhibitors;

(xx) 5-fluorouracil;

(xxi) curcumin;

(xxii) NF-κB inhibitors;

(xxiii) rosmarinic acid;

(xxiv) mitoguazone;

(xxv) tetrandrine;

(xxvi) a tyrosine kinase inhibitor;

(xxvii) an inhibitor of EGFR; and

(xxviii) an inhibitor of PARP;

wherein the substituted hexitol derivative acts as a chemosensitizer.

93. The composition of claim 92 wherein the substituted hexitol derivative is dianhydrogalactitol.

94. The composition of claim 83 wherein the composition comprises:

(a) a substituted hexitol derivative; and

(b) a therapeutic agent subject to chemopotentiation selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;

(iii) fraudulent nucleotides;

(iv) thymidylate synthetase inhibitors;

(v) signal transduction inhibitors;

(vi) a platinum analog selected from the group consisting of cisplatin, oxaliplatin, and another platinum analog;

(vii) alkylating agents;

(viii) anti-tubulin agents;

(ix) antimetabolites;

(x) berberine;

(xi) apigenin;

(xii) amonafide;

(xiii) colchicine or analogs;

(xiv) genistein;

(xv) etoposide;

(xvi) cytarabine;

(xvii) camptothecins;

(xviii) vinca alkaloids;

(xix) 5-fluorouracil;

(xx) curcumin;

(xxi) NF-κB inhibitors;

(xxii) rosmarinic acid;

(xxiii) mitoguazone;

(xxiv) tetrandrine;

(xxv) a tyrosine kinase inhibitor;

(xxvi) an inhibitor of EGFR; and

(xxvii) an inhibitor of PARP;

wherein the substituted hexitol derivative acts as a chemopotentiator.

95. The composition of claim 94 wherein the substituted hexitol derivative is dianhydrogalactitol.

96. The composition of claim 83 wherein the substituted hexitol derivative is subjected to a bulk drug product improvement, wherein the bulk drug product improvement is selected from the group consisting of:

(a) salt formation;

(b) preparation as a homogeneous crystal structure;

(c) preparation as a pure isomer;

(d) increased purity;

(e) preparation with lower residual solvent content; and

(f) preparation with lower residual heavy metal content.

97. The composition of claim 96 wherein the substituted hexitol derivative is dianhydrogalactitol.

98. The composition of claim 83 wherein the composition comprises a substituted hexitol derivative and a diluent, wherein the diluent is selected from the group consisting of:

(a) an emulsion;

(b) dimethylsulfoxide (DMSO);

(c) N-methylformamide (NMF)

(d) DMF;

(e) ethanol;

(f) benzyl alcohol;

(g) dextrose-containing water for injection;

(h) Cremophor;

(i) cyclodextrin; and

(j) PEG.

99. The composition of claim 98 wherein the substituted hexitol derivative is dianhydrogalactitol.

100. The composition of claim 83 wherein the composition comprises a substituted hexitol derivative and a solvent system, wherein the solvent system is selected from the group consisting of:

(a) an emulsion;

(b) dimethylsulfoxide (DMSO);

(c) N-methylformamide (NMF)

(d) DMF;

(e) ethanol;

(f) benzyl alcohol;

(g) dextrose-containing water for injection;

(h) Cremophor;

(i) cyclodextrin; and

(j) PEG.

101. The composition of claim 100 wherein the substituted hexitol derivative is dianhydrogalactitol.

102. The composition of claim 83 wherein the composition comprises a substituted hexitol derivative and an excipient, wherein the excipient is selected from the group consisting of:

(a) mannitol;

(b) albumin;

(c) EDTA;

(d) sodium bisulfite;

(e) benzyl alcohol;

(f) a carbonate buffer; and

(g) a phosphate buffer.

103. The composition of claim 102 wherein the substituted hexitol derivative is dianhydrogalactitol.

104. The composition of claim 83 wherein the substituted hexitol derivative is incorporated into a dosage form selected from the group consisting of:

(a) tablets;

(b) capsules;

(c) topical gels;

(d) topical creams;

(e) patches;

(f) suppositories; and

(g) lyophilized dosage fills.

105. The composition of claim 104 wherein the substituted hexitol derivative is dianhydrogalactitol.

106. The composition of claim 105 wherein the substituted hexitol derivative is incorporated into a dosage kit and packaging selected from the group consisting of amber vials to protect from light and stoppers with specialized coatings to improve shelf-life stability.

107. The composition of claim 106 wherein the substituted hexitol derivative is dianhydrogalactitol.

108. The composition of claim 83 wherein the composition comprises a substituted hexitol derivative and a drug delivery system selected from the group consisting of:

(a) nanocrystals;

(b) bioerodible polymers;

(c) liposomes;

(d) slow release injectable gels; and

(e) microspheres.

109. The composition of claim 108 wherein the substituted hexitol derivative is dianhydrogalactitol.

110. The composition of claim 83 wherein the substituted hexitol derivative is present in the composition in a drug conjugate form selected from the group consisting of:

(a) a polymer system;

(b) polylactides;

(c) polyglycolides;

(d) amino acids;

(e) peptides; and

(f) multivalent linkers.

111. The composition of claim 110 wherein the substituted hexitol derivative is dianhydrogalactitol.

112. The composition of claim 83 wherein the therapeutic agent is a modified substituted hexitol derivative and the modification is selected from the group consisting of:

(a) alteration of side chains to increase or decrease lipophilicity;

(b) addition of an additional chemical functionality to alter a property selected from the group consisting of reactivity, electron affinity, and binding capacity; and

(c) alteration of salt form.

113. The composition of claim 112 wherein the modified substituted hexitol derivative is a modified dianhydrogalactitol.

114. The composition of claim 83 wherein the substituted hexitol derivative is in the form of a prodrug system, wherein the prodrug system is selected from the group consisting of:

(a) enzyme sensitive esters;

(b) dimers;

(c) Schiff bases;

(d) pyridoxal complexes; and

(e) caffeine complexes.

115. The composition of claim 114 wherein the substituted hexitol derivative is dianhydrogalactitol.

116. The composition of claim 83 wherein the composition comprises a substituted hexitol derivative and at least one additional therapeutic agent to form a multiple drug system, wherein the at least one additional therapeutic agent is selected from the group consisting of:

(a) an inhibitor of multi-drug resistance;

(b) a specific drug resistance inhibitor;

(c) a specific inhibitor of a selective enzyme;

(d) a signal transduction inhibitor;

(e) an inhibitor of a repair enzyme; and

(f) a topoisomerase inhibitor with non-overlapping side effects.

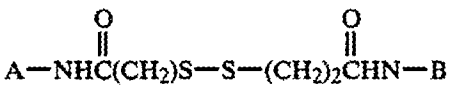
117. The composition of claim 116 wherein the substituted hexitol derivative is dianhydrogalactitol.

118. The composition of claim 83 wherein the composition comprises a substituted hexitol derivative and an agent to counteract myelosuppression, wherein the agent to counteract myelosuppression is a dithiocarbamate.

119. The composition of claim 118 wherein the substituted hexitol derivative is dianhydrogalactitol.

120. The composition of claim 83 wherein the composition comprises a substituted hexitol derivative and an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier, wherein the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier is selected from the group consisting of:

(a) a chimeric peptide of the structure of Formula (D-III):



(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric

peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):

$$A\text{-}NH(CH_2)_2S\text{-}S\text{-}B \text{ (cleavable linkage)}$$

(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):

$$A\text{-}NH{=}CH(CH_2)_3CH{=}NH\text{-}B \text{ (non-cleavable linkage)}$$

(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

(b) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(c) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(d) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(e) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

121. The composition of claim 120 wherein the substituted hexitol derivative is dianhydrogalactitol.

122. A method of treating non-small-cell lung carcinoma (NSCLC) comprising the step of administering a therapeutically effective quantity of a substituted hexitol derivative to a patient suffering from NSCLC.

123. The method of claim 122 wherein the substituted hexitol derivative is selected from the group consisting of galactitols, substituted galacitols, dulcitols, and substituted dulcitols.

124. The method of claim 123 wherein the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol.

125. The method of claim 124 wherein the substituted hexitol derivative is dianhydrogalactitol.

126. The method of claim 125 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 1 mg/m^2 to about 40 mg/m^2.

127. The method of claim 126 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 5 mg/m^2 to about 25 mg/m^2.

128. The method of claim 125 wherein the dianhydrogalactitol is administered by a route selected from the group consisting of intravenous and oral.

129. The method of claim 122 further comprising a step selected from the group consisting of:

(a) administering a therapeutically effective dose of ionizing radiation;

(b) administering a therapeutically effective quantity of temozolomide;

(c) administering a therapeutically effective quantity of bevacizumab;

(d) administering a therapeutically effective quantity of a corticosteroid;

(e) administering a therapeutically effective quantity of at least one chemotherapeutic agent selected from the group consisting of lomustine, a platinum-containing chemotherapeutic agent, vincristine, and cyclophosphamide;

(f) administering a therapeutically effective quantity of a tyrosine kinase inhibitor; and

(g) administering a therapeutically effective quantity of an EGFR inhibitor.

130. The method of claim 122 wherein the method further comprises the step of administering a therapeutically effective quantity of a platinum-containing chemotherapeutic agent and wherein the platinum-containing chemotherapeutic agent is selected from the group consisting of cisplatin, carboplatin, iproplatin, oxaliplatin, tetraplatin, satraplatin, picoplatin, nedaplatin, and triplatin.

131. The method of claim 130 wherein the administration of the substituted hexitol derivative together with the platinum-containing chemotherapeutic agent is a component of standard platinum doublet strategy.

132. The method of claim 125 wherein the dianhydrogalactitol substantially suppresses the growth of cancer stem cells (CSCs).

133. The method of claim 125 wherein the dianhydrogalactitol is effective in suppressing the growth of cancer cells possessing O^6-methylguanine-DNA methyltransferase (MGMT)-driven drug resistance.

134. The method of claim 125 wherein the dianhydrogalactitol is effective in suppressing the growth of cancer cells resistant to temozolomide.

135. The method of claim 129 wherein the method comprises administering a therapeutically effective quantity of an EGFR inhibitor and wherein the EGFR inhibitor affects wild-type binding sites.

136. The method of claim 129 wherein the method comprises administering a therapeutically effective quantity of an EGFR inhibitor and wherein the EGFR inhibitor affects mutated binding sites.

137. The method of claim 136 wherein the EGFR inhibitor affects EGFR Variant III.

138. The method of claim 122 wherein the method further comprises administering to the patient a therapeutically effective quantity of an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier.

139. The method of claim 122 wherein the method further comprises administering to the patient a therapeutically effective quantity of an agent that counteracts myelosuppression.

140. The method of claim 125 wherein the effect of administration of dianhydrogalactitol and a platinum-containing agent selected from the group consisting of cisplatin and oxaliplatin is at least additive.

141. The method of claim 125 wherein dianhydrogalactitol is administered to a subject in which at least one of p53 or p25 is affected by a loss-of-function mutation.

142. A method of treating ovarian cancer comprising the step of administering a therapeutically effective quantity of a substituted hexitol derivative to a patient suffering from ovarian cancer.

143. The method of claim 142 wherein the substituted hexitol derivative is selected from the group consisting of galactitols, substituted galacitols, dulcitols, and substituted dulcitols.

144. The method of claim 143 wherein the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol.

145. The method of claim 144 wherein the substituted hexitol derivative is dianhydrogalactitol.

146. The method of claim 145 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 1 mg/m^2 to about 40 mg/m^2.

147. The method of claim 146 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 5 mg/m^2 to about 25 mg/m^2.

148. The method of claim 145 wherein the dianhydrogalactitol is administered by a route selected from the group consisting of intravenous and oral.

149. The method of claim 146 wherein the ovarian cancer is a cisplatin-resistant wild-type p53 cancer.

150. The method of claim 142 wherein the method further comprises the step of administering a therapeutically effective quantity of a platinum-containing chemotherapeutic agent and wherein the platinum-containing chemotherapeutic agent is selected from the group consisting of cisplatin, carboplatin, iproplatin, oxaliplatin, tetraplatin, satraplatin, picoplatin, nedaplatin, and triplatin.

151. The method of claim 142 wherein the method further comprises the step of administering a therapeutically effective quantity of an antineoplastic agent selected from paclitaxel, docetaxel, topotecan, gemcitabine, bleomycin, etoposide, doxorubicin, tamoxifen, letrozole, olaparib, selumetinib, mTOR inhibitors, PI3 kinase inhibitors, and trichostatin A.

152. The method of claim 142 wherein the substituted hexitol derivative suppresses the growth of cancer stem cells.

153. The method of claim 142 wherein the substituted hexitol derivative suppresses the growth of cancer cells possessing O^6-methylguanine-DNA methyltransferase (MGMT)-driven drug resistance.

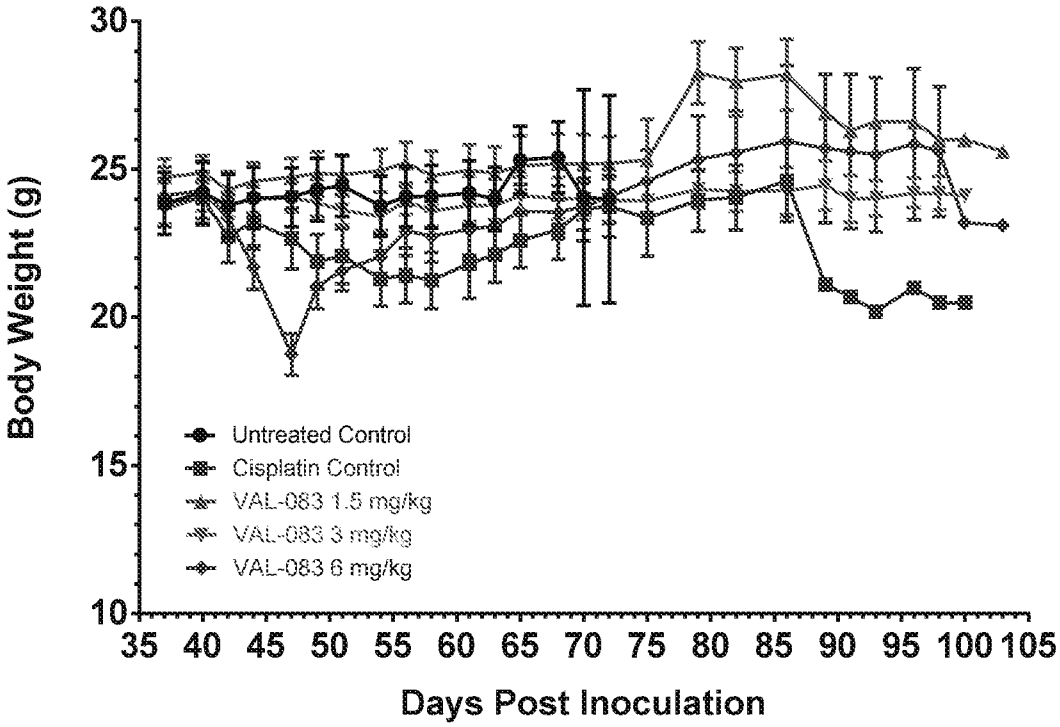
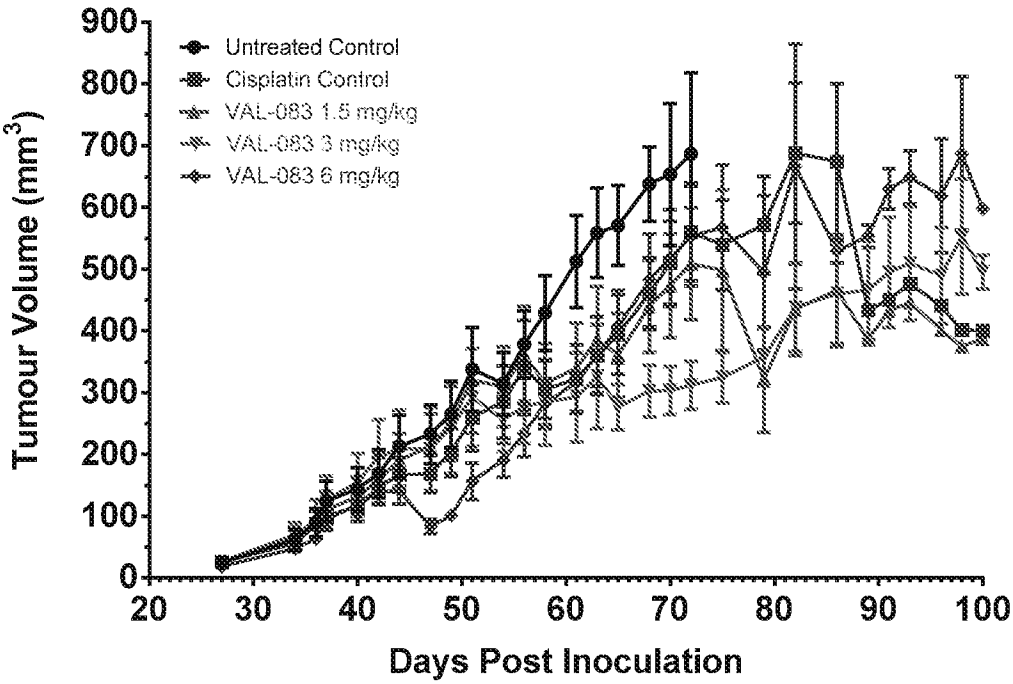

Body Weight (g)
30
25
20
15
10
35 40 45 50 55 60 65 70 75 80 85 90 95 100 105
Days Post Inoculation
Untreated Control
Cisplatin Control
VAL-083 1.5 mg/kg
VAL-083 3 mg/kg
VAL-083 6 mg/kg

Figure 1


Untreated Control
Cisplatin Control
VAL-083 1.5 mg/kg
VAL-083 3 mg/kg
VAL-083 6 mg/kg
Tumour Volume (mm3)
Days Post Inoculation
0
100
200
300
400
500
600
700
800
900
20
30
40
50
60
70
80
90
100

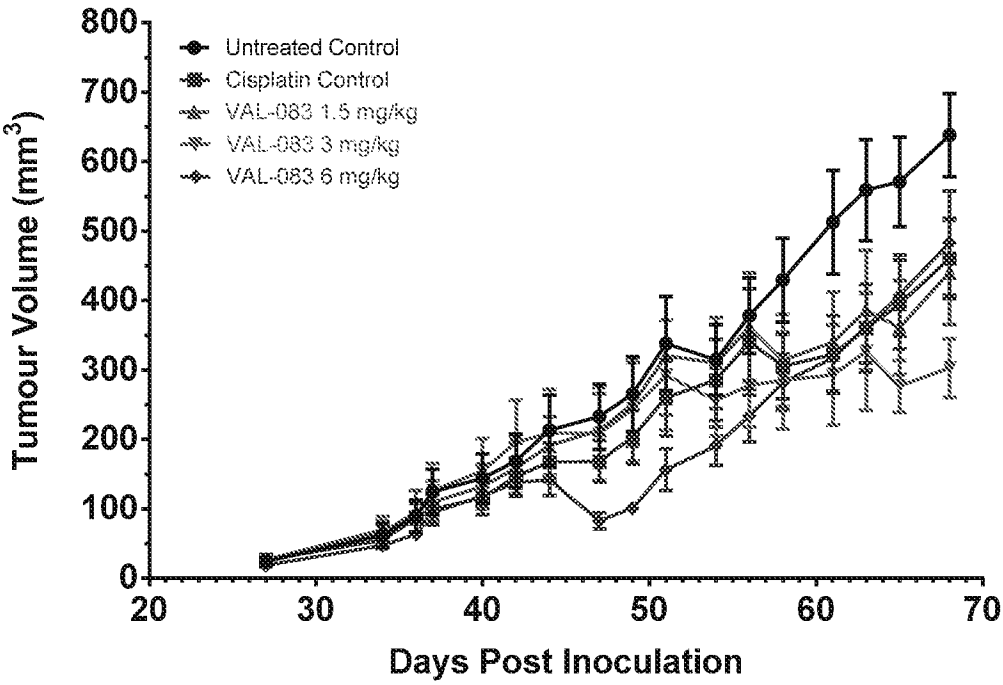

Untreated Control
Cisplatin Control
VAL-083 1.5 mg/kg
VAL-083 3 mg/kg
VAL-083 6 mg/kg
Tumour Volume (mm3)
Days Post Inoculation
0
100
200
300
400
500
600
700
800
20
30
40
50
60
70

Figure 2

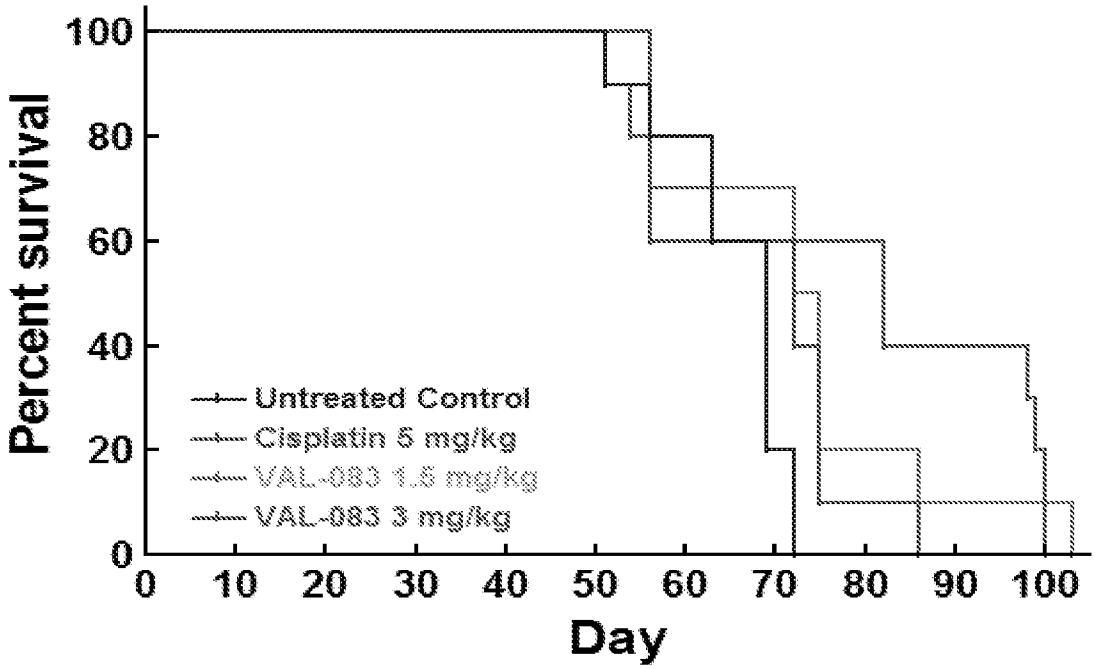

Percent survival
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
Day
Untreated Control
Cisplatin 5 mg/kg
VAL-083 1.5 mg/kg
VAL-083 3 mg/kg

Figure 3

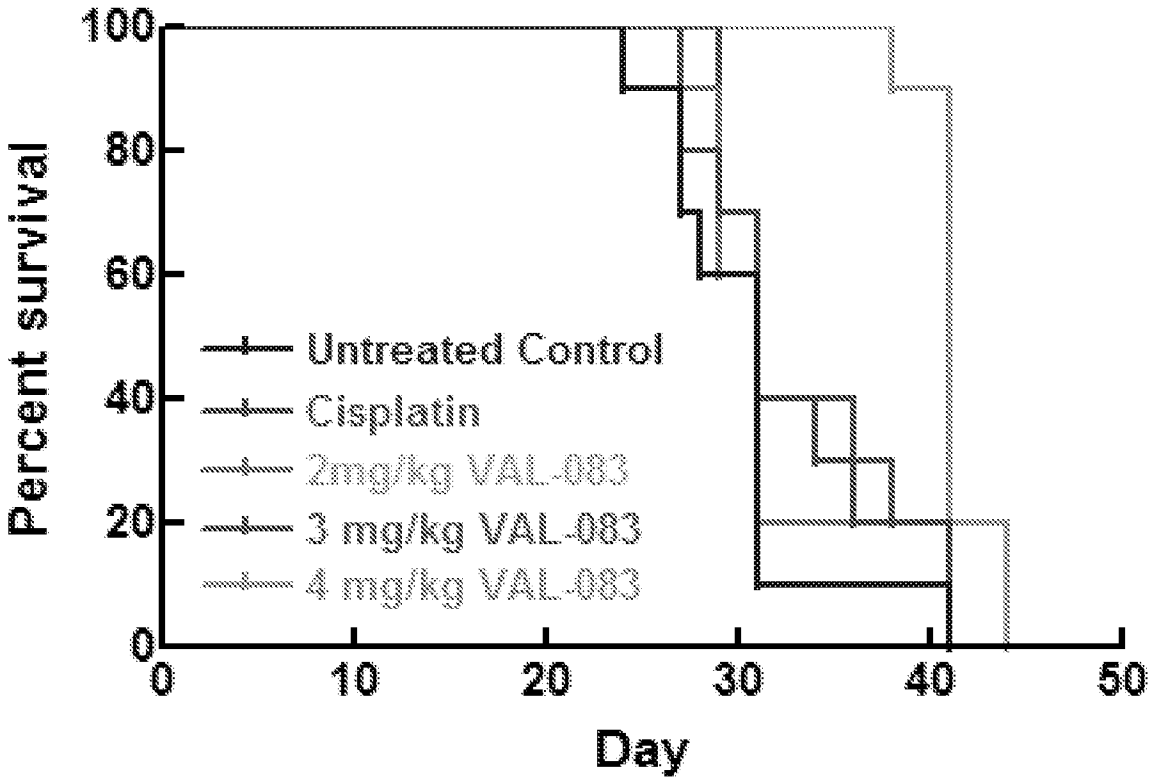

Percent survival
100
80
60
40
20
0
0
10
20
30
40
50
Day
Untreated Control
Cisplatin
2mg/kg VAL-083
3 mg/kg VAL-083
4 mg/kg VAL-083

Figure 4

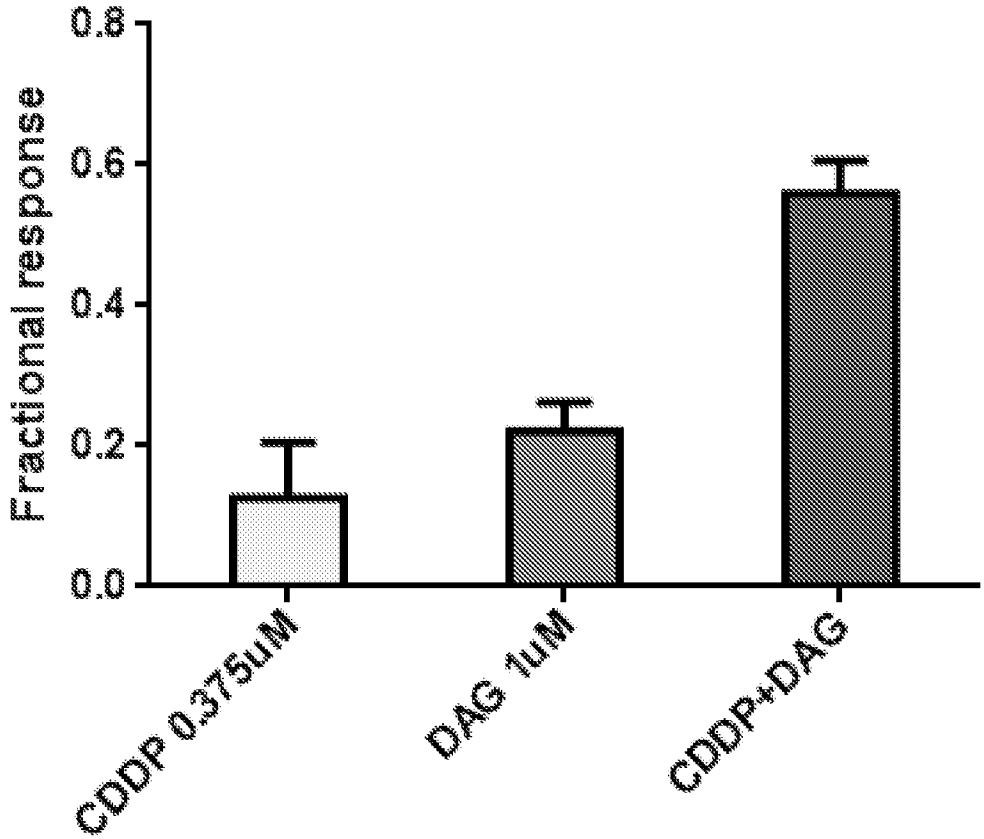

Fractional response
0.8
0.6
0.4
0.2
0.0
CDDP 0.375uM
DAG 1uM
CDDP+DAG

Figure 5A

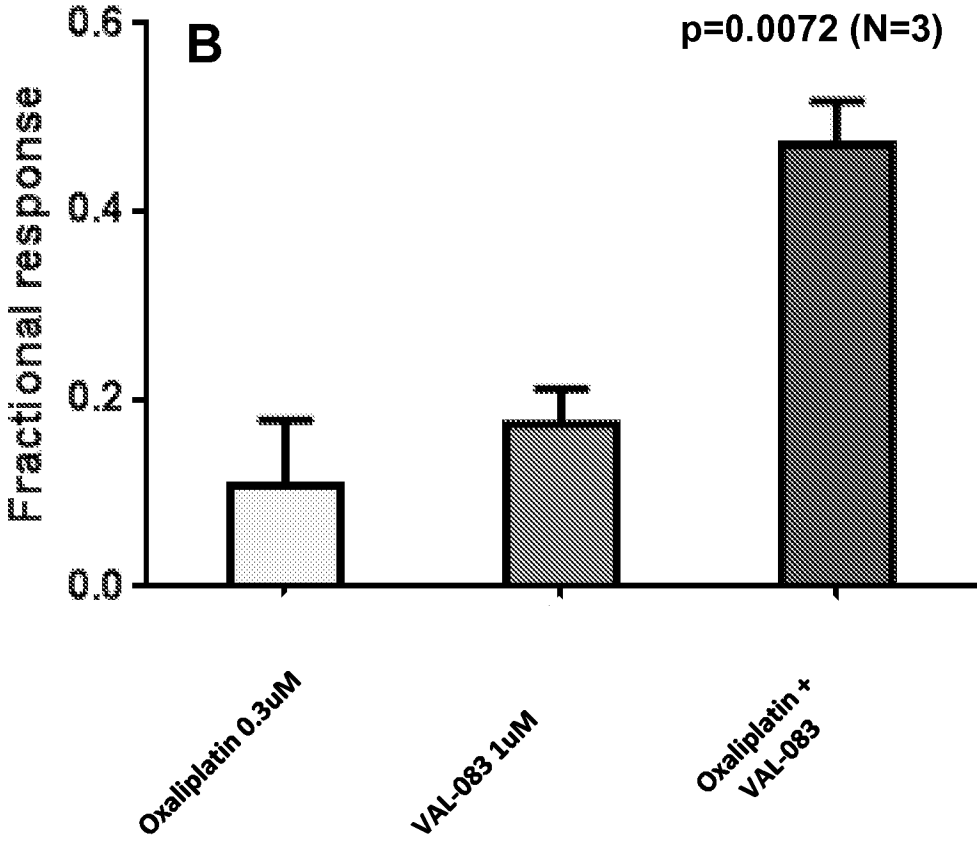

B
p=0.0072 (N=3)
Fractional response
0.6
0.4
0.2
0.0
Oxaliplatin 0.3uM
VAL-083 1uM
Oxaliplatin + VAL-083

Figure 5B

Figure 6A

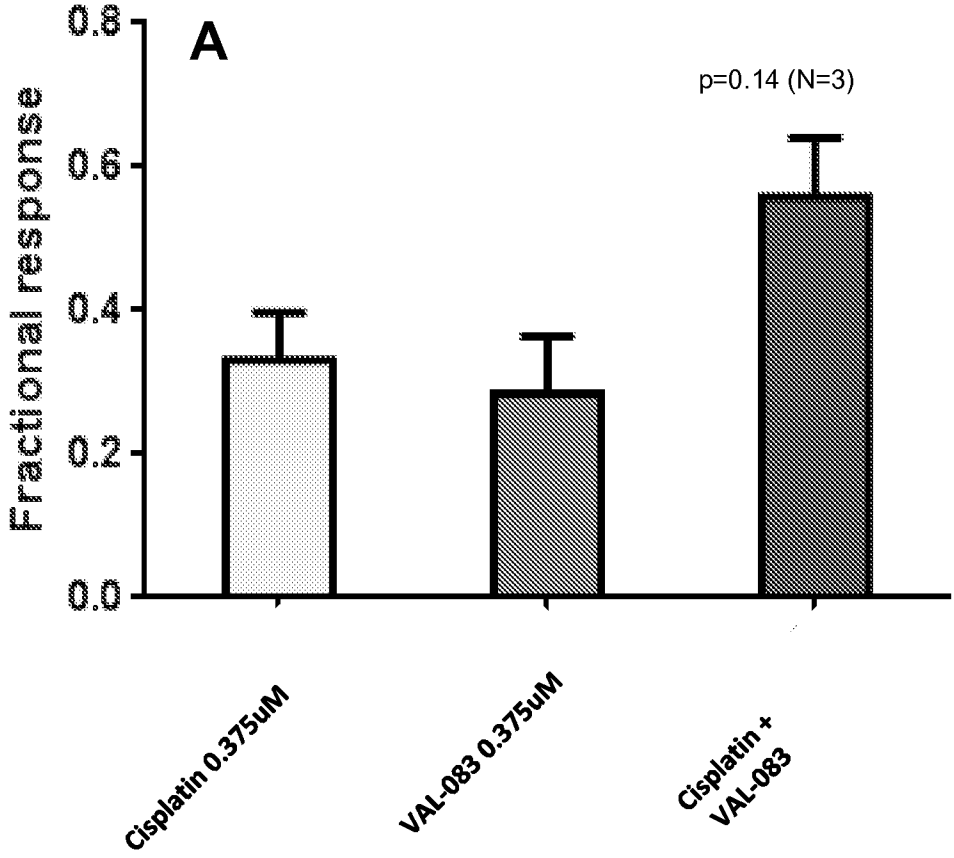
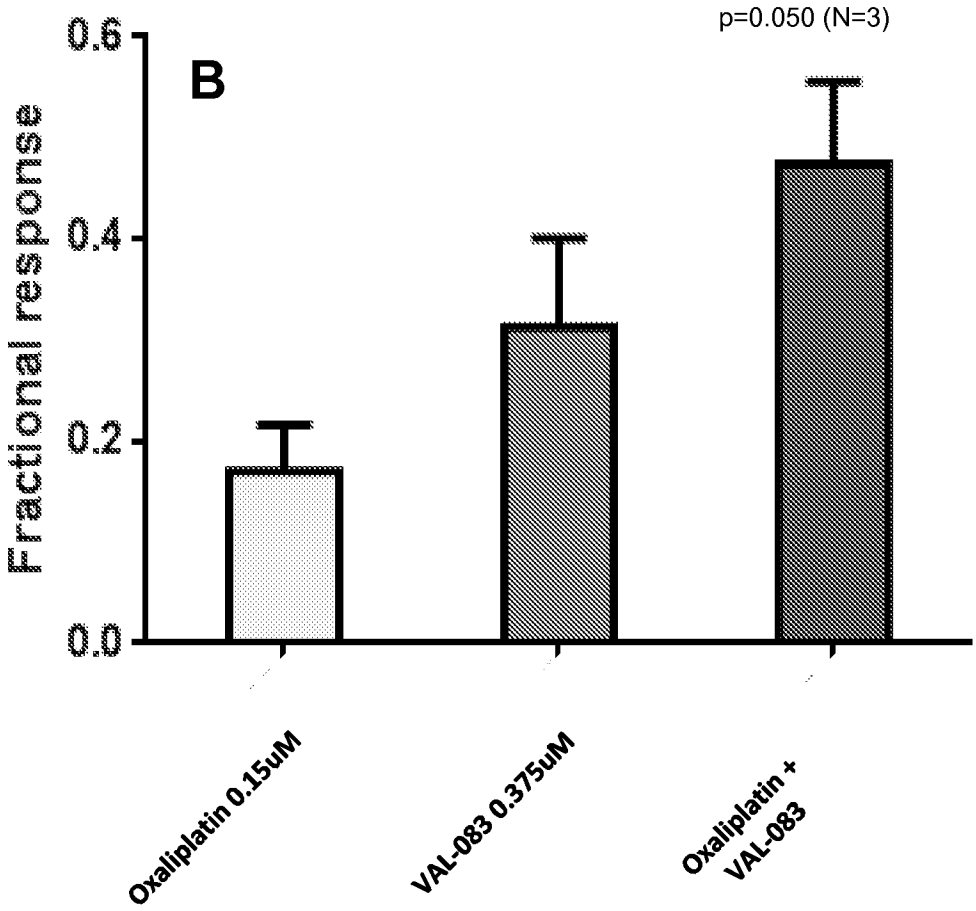

A
p=0.14 (N=3)
Fractional response
0.8
0.6
0.4
0.2
0.0
Cisplatin 0.375uM
VAL-083 0.375uM
Cisplatin + VAL-083

Figure 6B


p=0.050 (N=3)
B
Fractional response
0.6
0.4
0.2
0.0
Oxaliplatin 0.15uM
VAL-083 0.375uM
Oxaliplatin + VAL-083

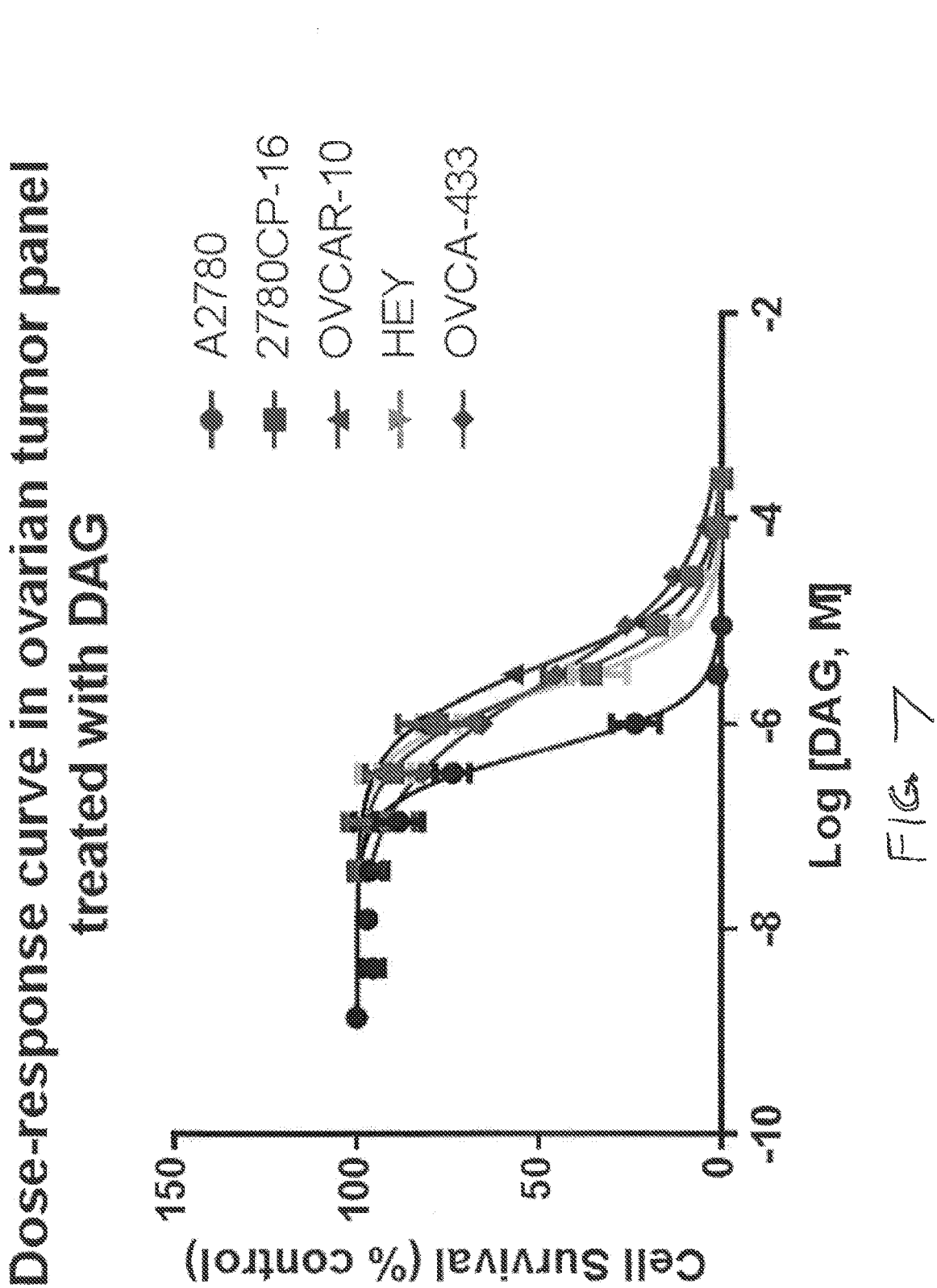

Dose-response curve in ovarian tumor panel
treated with DAG
A2780
2780CP-16
OVCAR-10
HEY
OVCA-433
Cell Survival (% control)
150
100
50
0
-10
-8
-6
-4
-2
Log [DAG, M]

FIG 7

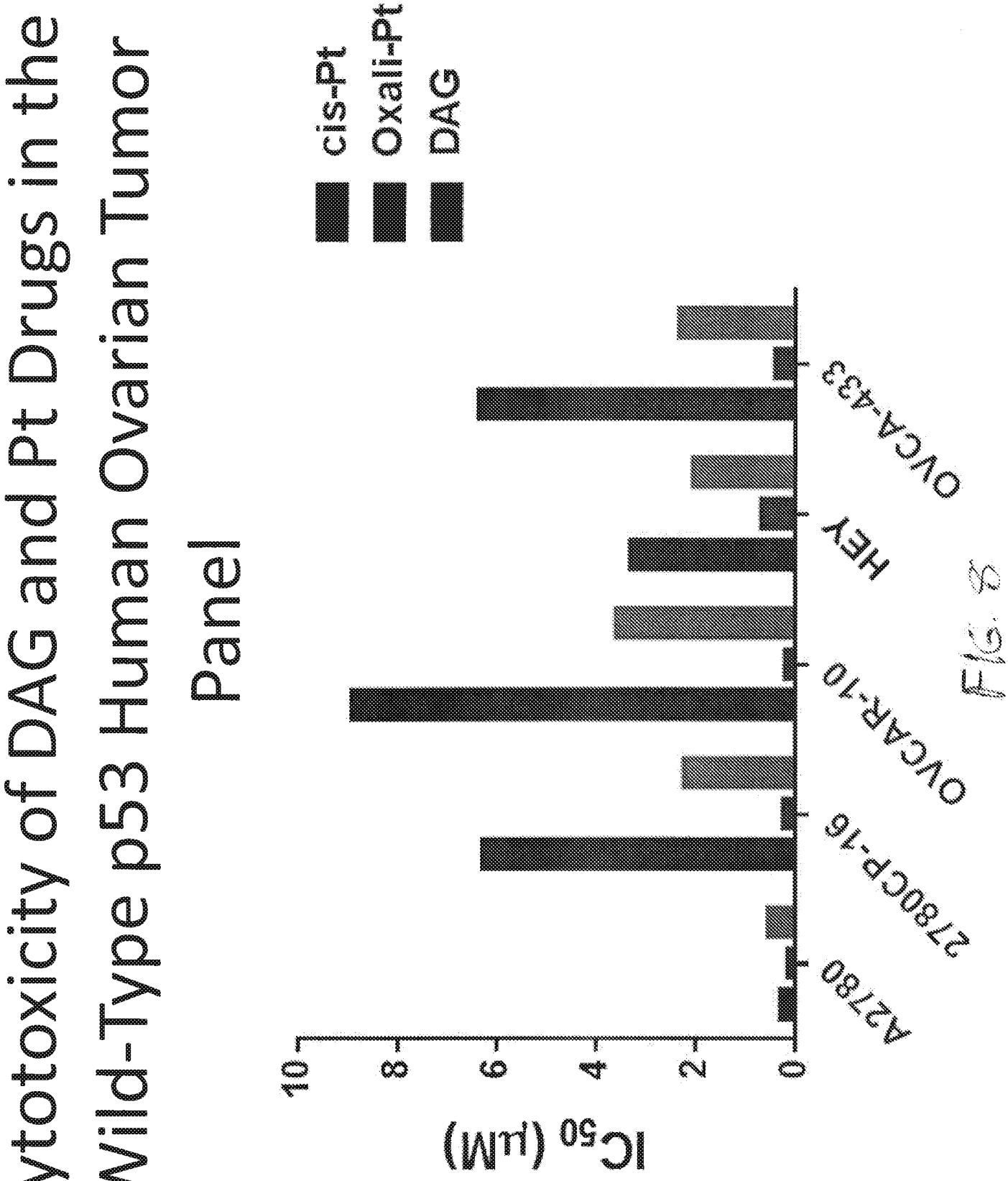

Cytotoxicity of DAG and Pt Drugs in the Wild-Type p53 Human Ovarian Tumor Panel
cis-Pt
Oxali-Pt
DAG
IC50 (μM)
0
2
4
6
8
10
A2780
2780CP-16
OVCAR-10
HEY
OVCA-433

Fig 8

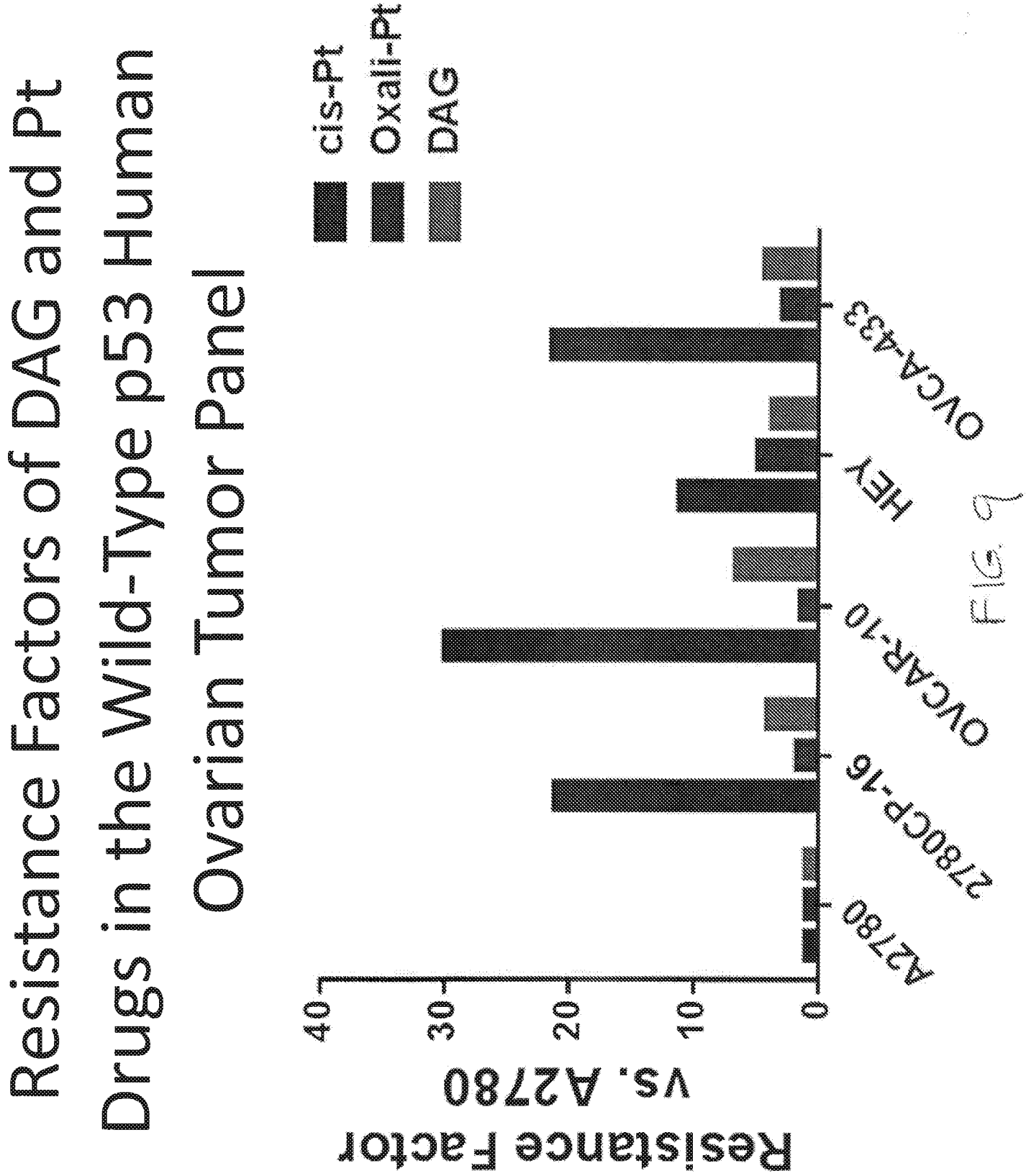
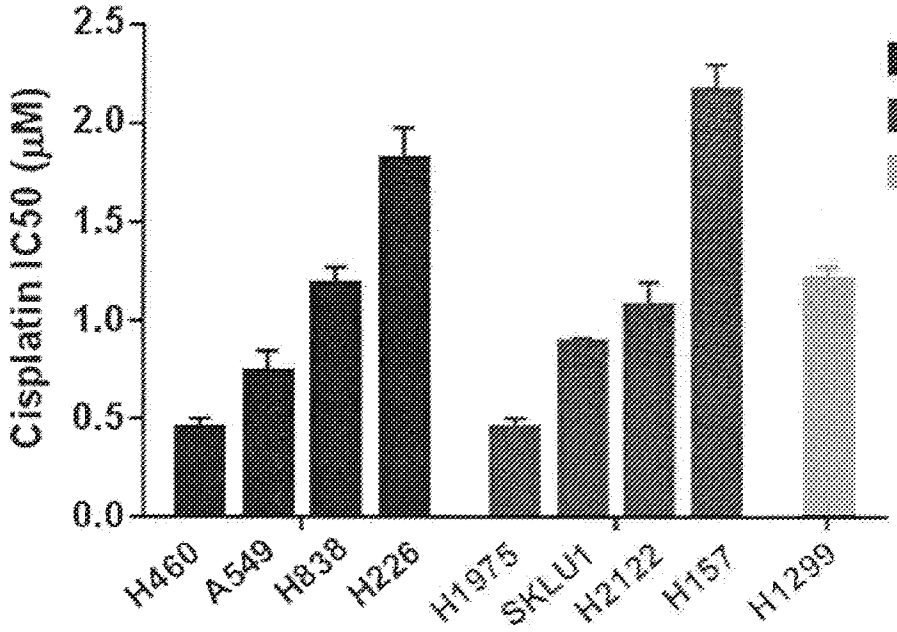

Resistance Factors of DAG and Pt Drugs in the Wild-Type p53 Human Ovarian Tumor Panel
cis-Pt
Oxali-Pt
DAG
Resistance Factor vs. A2780
40
30
20
10
0
A2780
2780CP-16
OVCAR-10
HEY
OVCA-433

FIG. 9

Cytotoxicity of Cisplatin and Relative Resistance in Human NSCLC Tumor Panel



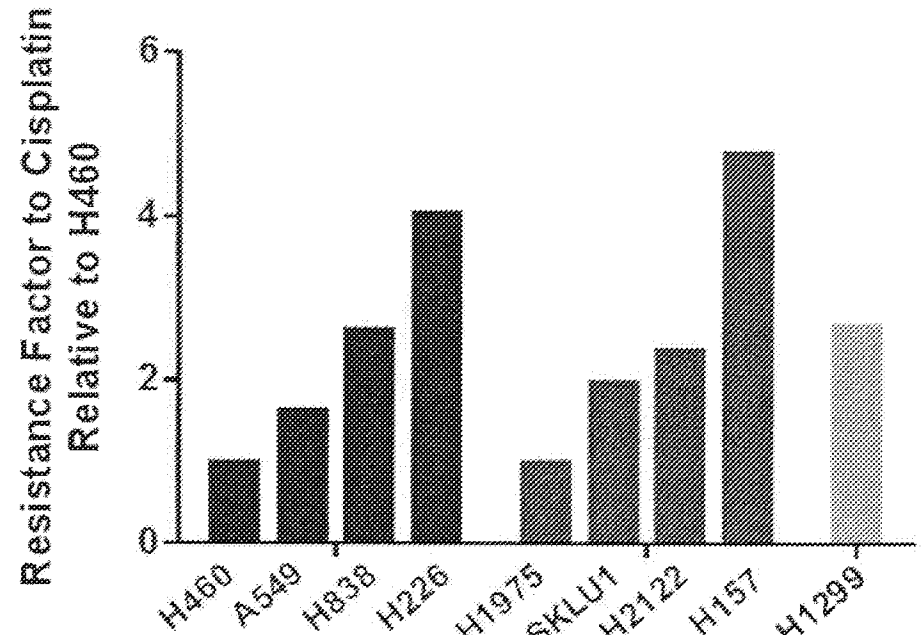
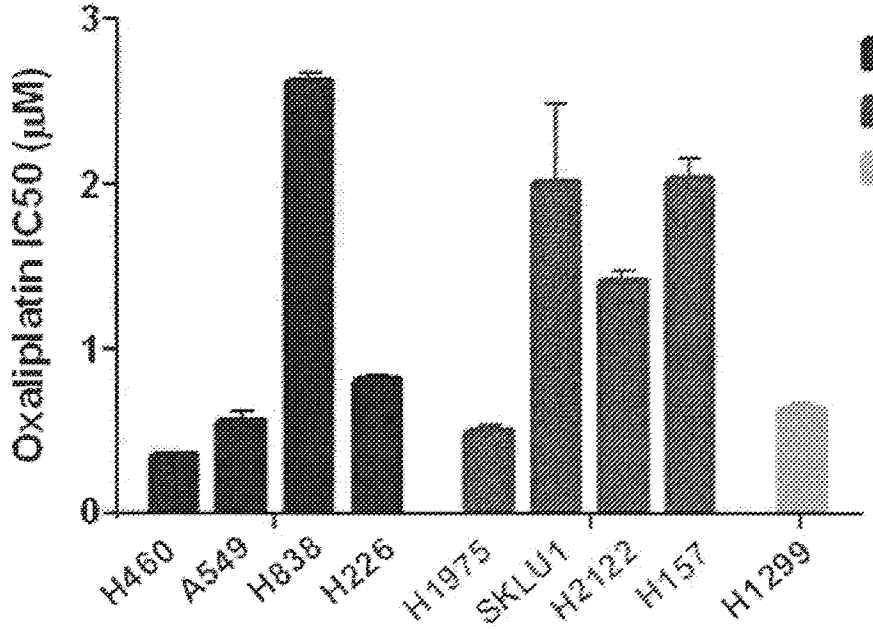


FIG. 10

Cytotoxicity of Oxaliplatin and Relative Resistance in Human NSCLC Tumor Panel



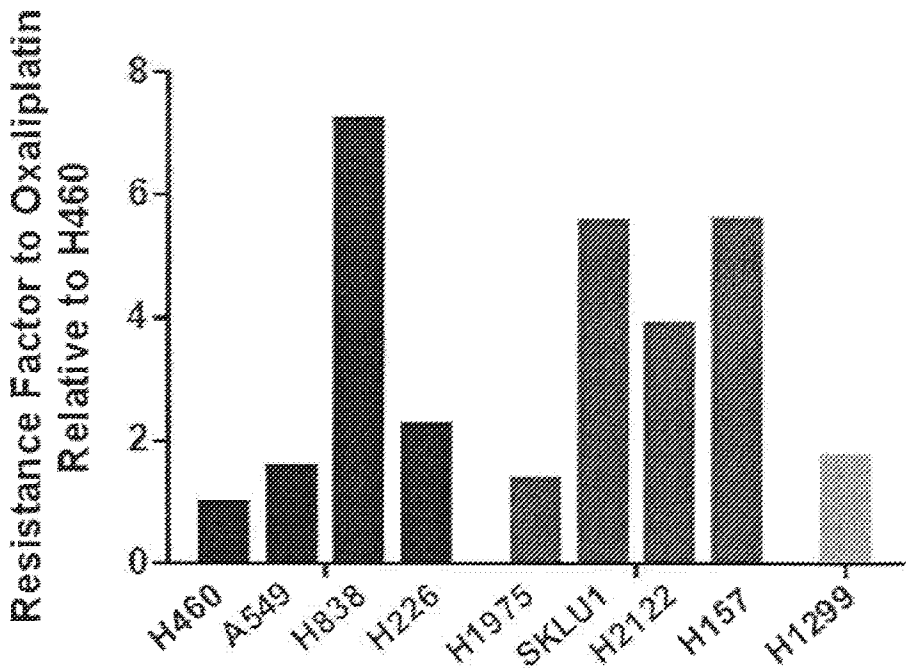


FIG. 11

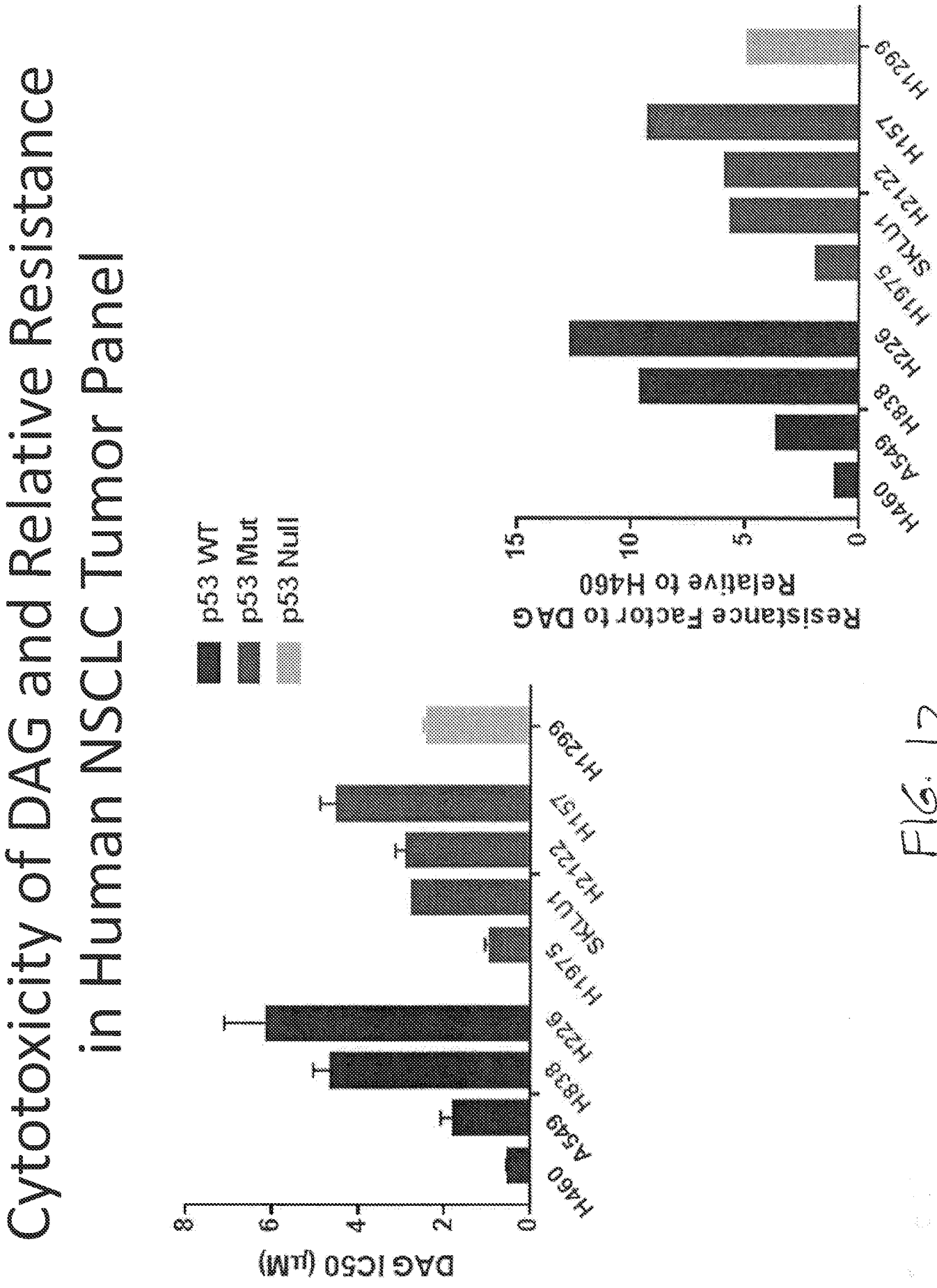

Cytotoxicity of DAG and Relative Resistance
in Human NSCLC Tumor Panel
p53 WT
p53 Mut
p53 Null
DAG IC50 (μM)
0
2
4
6
8
H460
A549
H838
H226
H1975
SKLU1
H2122
H157
H1299
Resistance Factor to DAG
Relative to H460
0
5
10
15
H460
A549
H838
H226
H1975
SKLU1
H2122
H157
H1299

Fig. 12

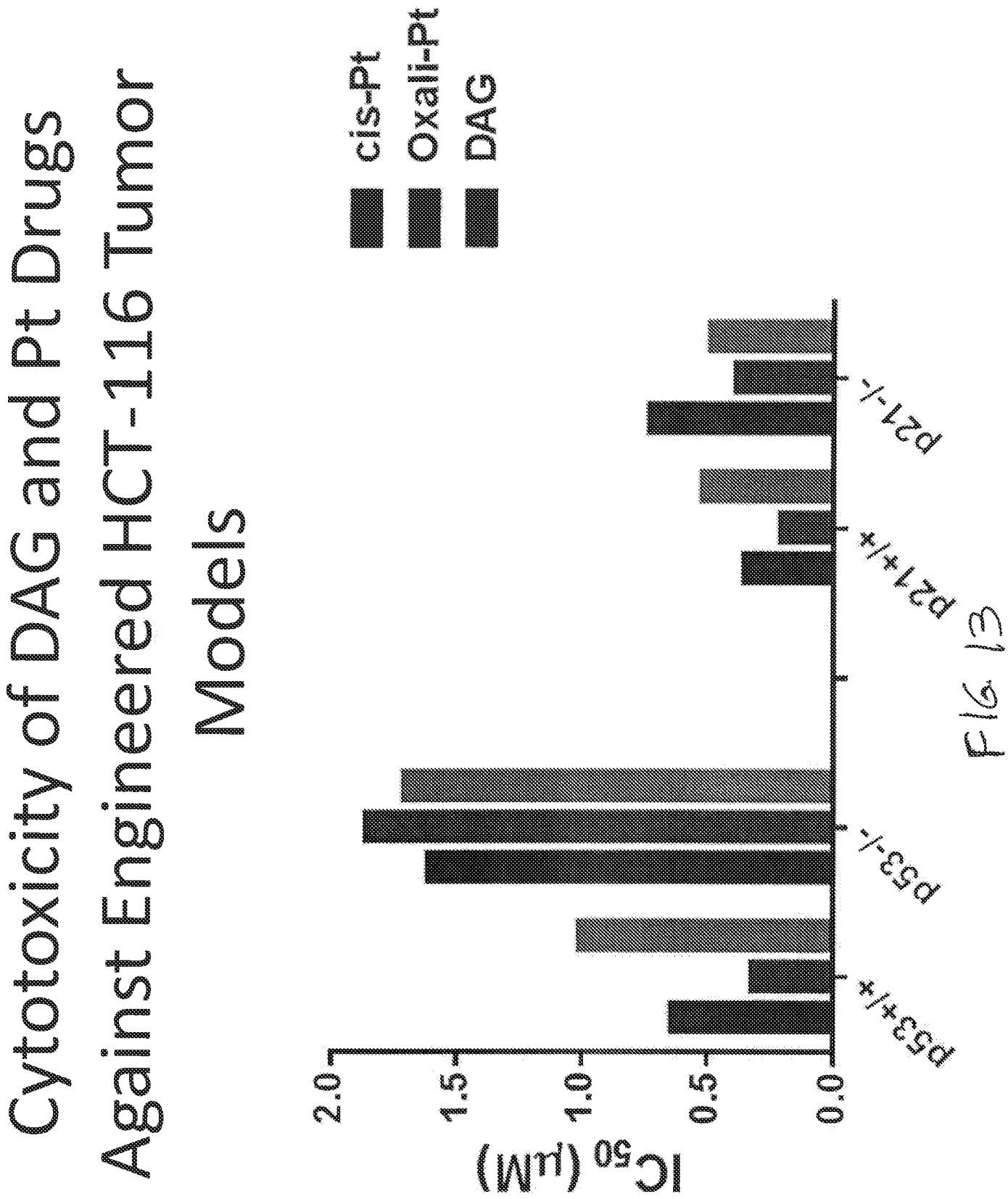

Cytotoxicity of DAG and Pt Drugs
Against Engineered HCT-116 Tumor
Models
cis-Pt
Oxali-Pt
DAG
IC50 (μM)
2.0
1.5
1.0
0.5
0.0
p53+/+
p53-/-
p21+/+
p21-/-

Fig 13

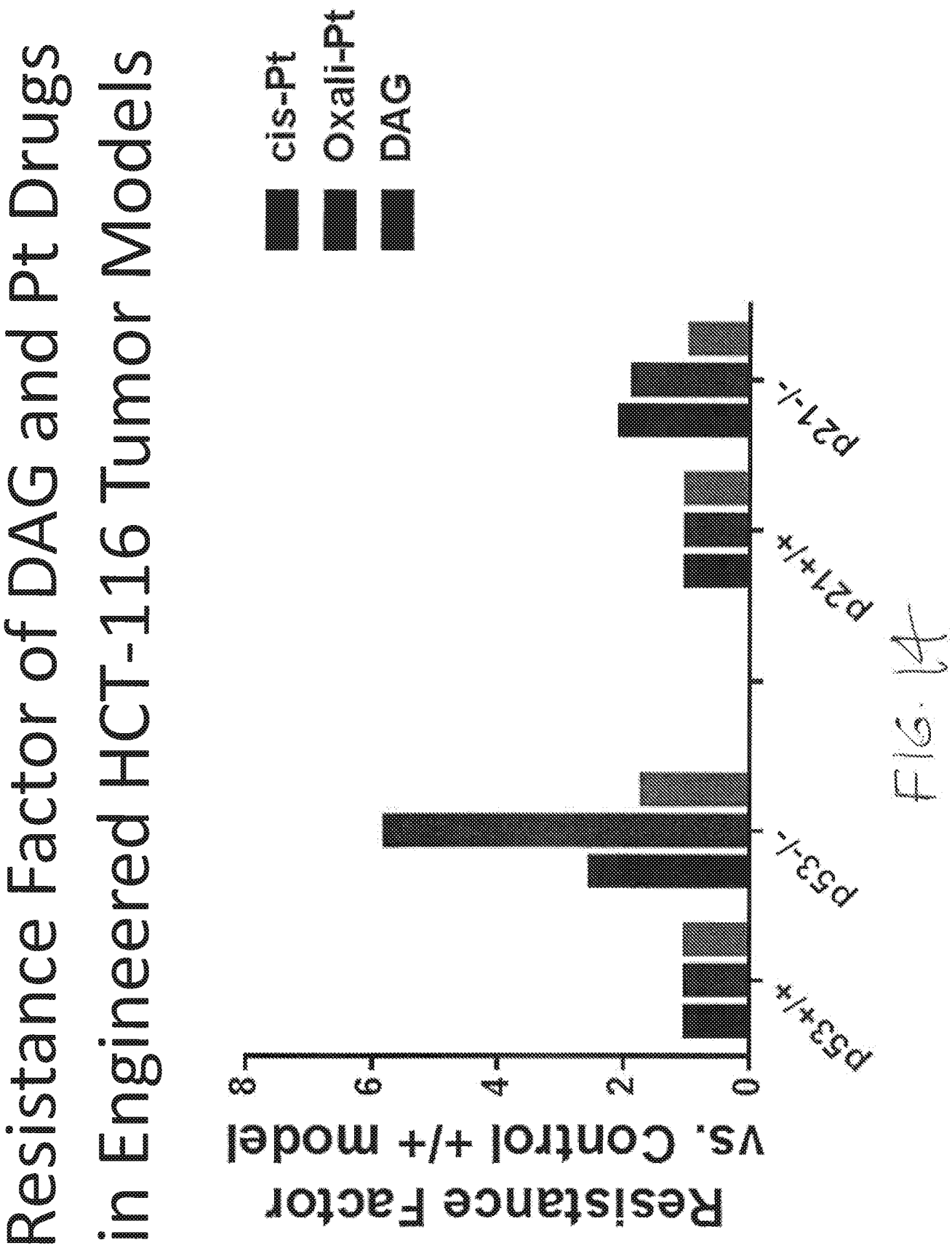
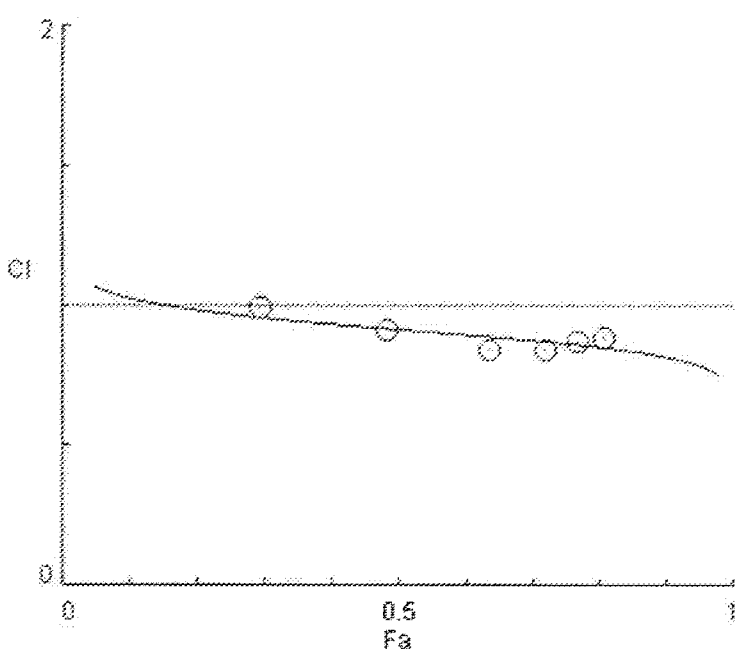

Resistance Factor of DAG and Pt Drugs
in Engineered HCT-116 Tumor Models
cis-Pt
Oxali-Pt
DAG
Resistance Factor
vs. Control +/+ model
0
2
4
6
8
p53+/+
p53-/-
p21+/+
p21-/-

Fig. 14

Combination Index of DAG with Cisplatin or Oxaliplatin in Human A549 NSCLC Model

Combination of CDDP and DAG

Note: Each data point is a mean of 4 independent determinations



CI: DAG + CisPt	
ED50	0.91697
ED75	0.86643
ED90	0.81882
ED95	0.78802

CI: DAG + OxPt	
ED50	1.05625
ED75	0.90984
ED90	0.78388
ED95	0.70840

Combination of Oxaliplatin and DAG

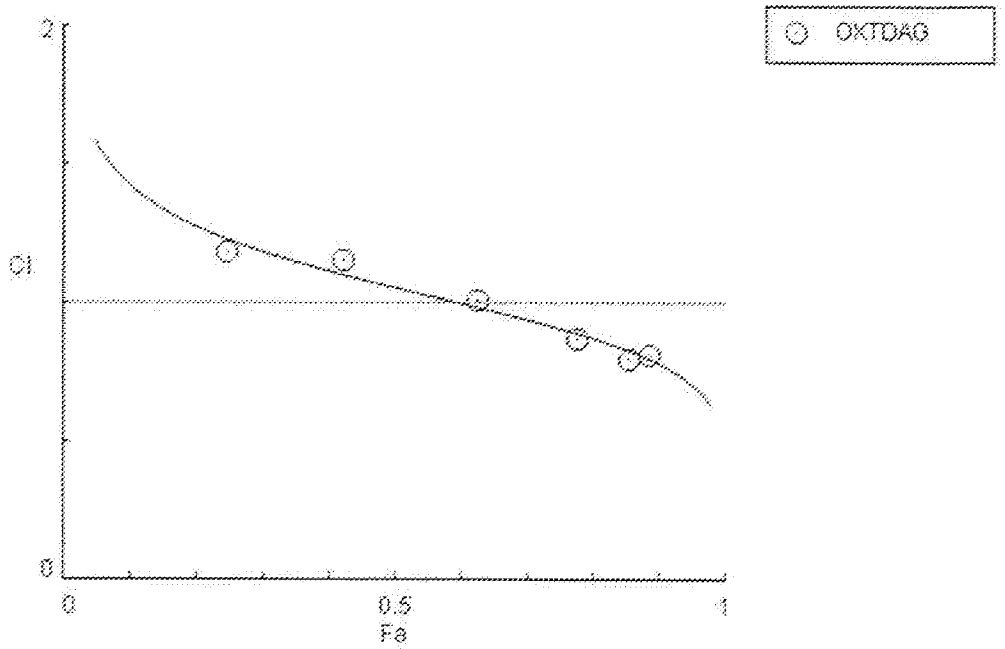


FIG. 15

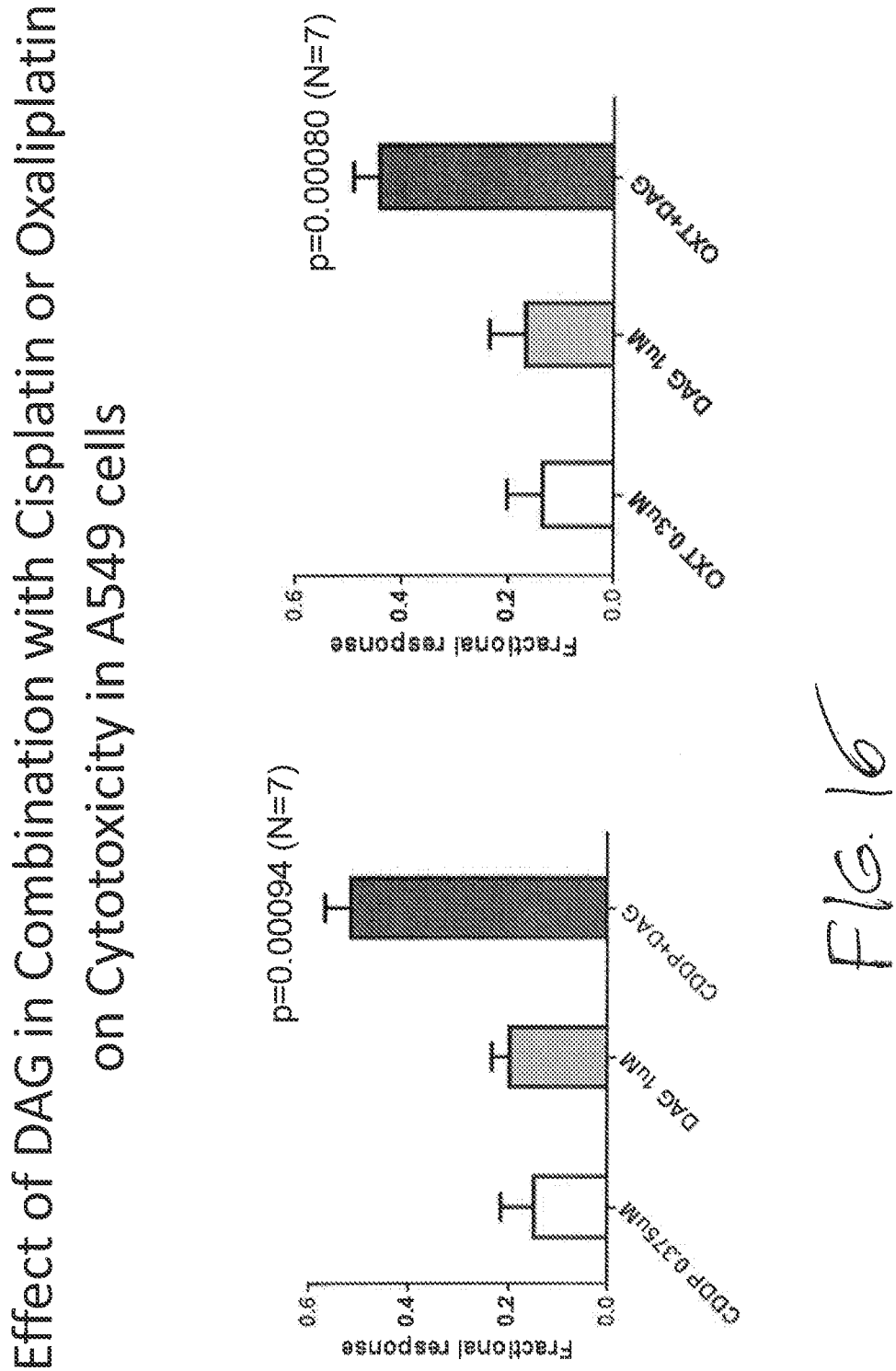

The Effect of DAG in Combination with Cisplatin or Oxaliplatin on Cytotoxicity in A549 cells
p=0.00094 (N=7)
Fractional response
0.0
0.2
0.4
0.6
CDDP 0.375um
DAG 1uM
CDDP+DAG
p=0.00080 (N=7)
Fractional response
0.0
0.2
0.4
0.6
OXT 0.3uM
DAG 1uM
OXT+DAG

FIG. 16

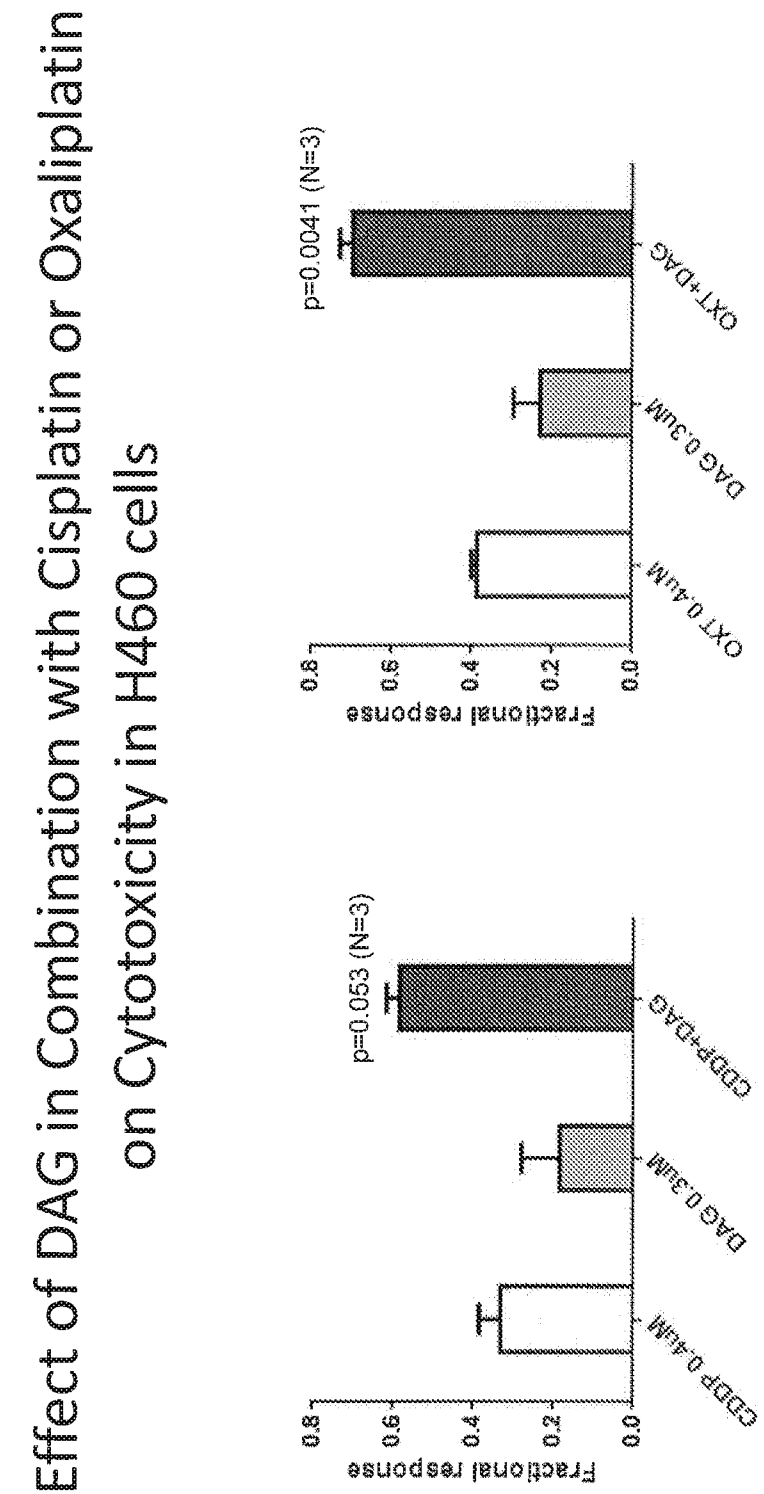

The Effect of DAG in Combination with Cisplatin or Oxaliplatin on Cytotoxicity in H460 cells
p=0.053 (N=3)
Fractional response
0.0
0.2
0.4
0.6
0.8
CDDP 0.4uM
DAG 0.3uM
CDDP+DAG
p=0.0041 (N=3)
Fractional response
0.0
0.2
0.4
0.6
0.8
OXT 0.4uM
DAG 0.3uM
OXT+DAG

FIG. 17

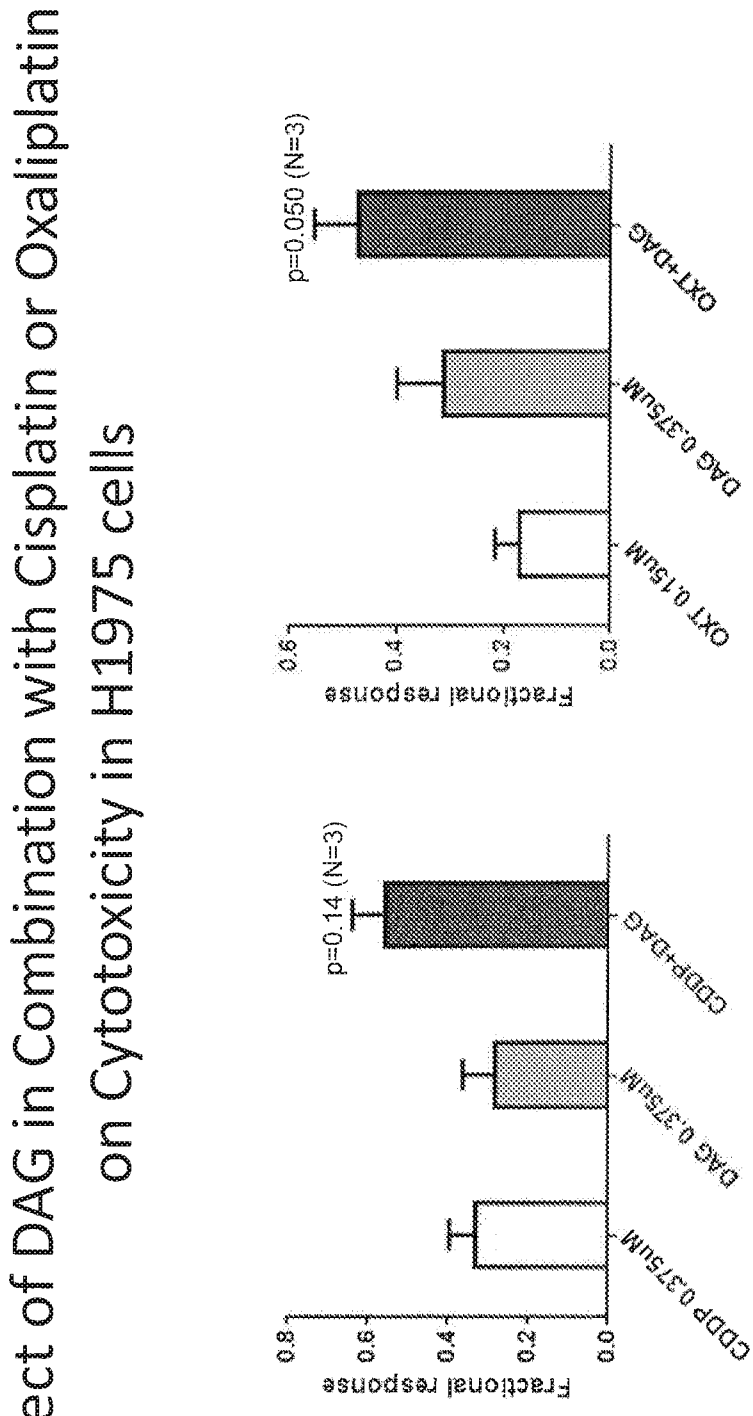

The Effect of DAG in Combination with Cisplatin or Oxaliplatin on Cytotoxicity in H1975 cells
p=0.050 (N=3)
OXT+DAG
DAG 0.375uM
OXT 0.15uM
Fractional response
0.0
0.2
0.4
0.6
p=0.14 (N=3)
CDDP+DAG
DAG 0.375uM
CDDP 0.375uM
Fractional response
0.0
0.2
0.4
0.6
0.8

FIG. 1B