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(54) Title: METHOD FOR TREATING DISEASES USING HSP90-INHIBITING AGENTS IN COMBINATION WITH ANTIMITOTICS

(57) Abstract: The present invention provides a method for treating cancer. The method involves the administration of an HSP90 inhibitor and an antimetabolic, where the combined administration provides a synergistic effect. In one aspect of the invention, a method of treating cancer is provided where a subject is treated with a dose of an HSP90 inhibitor in one step and a dose of an antimetabolic in another step. In another aspect of the invention, a method of treating cancer is provided where a subject is first treated with a dose of an HSP90 inhibitor and subsequently treated with a dose of an antimetabolic. In another aspect of the invention, a method of treating cancer is provided where a subject is first treated with a dose of an antimetabolic and subsequently treated with a dose of an HSP90 inhibitor.



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**METHOD FOR TREATING DISEASES USING HSP90-INHIBITING  
AGENTS IN COMBINATION WITH ANTIMITOTICS**

CROSS REFERENCE TO RELATED U.S. PATENT APPLICATIONS

5 [0001] The present application claims the benefit of Provisional Patent Application No. 60/474,906, which was filed May 30, 2003, under 35 U.S.C. § 119(e). The provisional application is hereby incorporated-by-reference into this application for all purposes.

10 BACKGROUND OF THE INVENTION

*Field of the Invention*

[0002] This invention relates to methods for treating cancer in which an inhibitor of Heat Shock Protein 90 (“HSP90”) is combined with an antimitotic. More particularly, this invention relates to combinations of the HSP90 inhibitor geldanamycin and its  
15 derivatives, especially 17-alkylamino-17-desmethoxygeldanamycin (“17-AAG”) and 17-(2-dimethylaminoethyl)amino-17-desmethoxygeldanamycin (“17-DMAG”), with an antimitotic (*e.g.*, docetaxel, discodermolide, vinblastine, vincristine, vindesine, and epothilone D).

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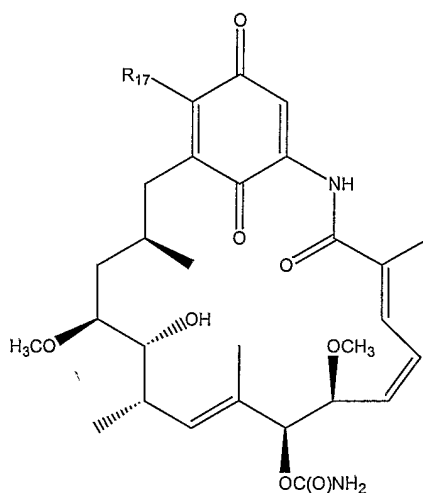
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*Discussion*

[0045] Geldanamycin (figure below,  $R_{17} = -OCH_3$ ) is a benzoquinone ansamycin polyketide isolated from *Streptomyces geldanus*. Although originally discovered by screening microbial extracts for antibacterial and antiviral activity, geldanamycin was later found to be cytotoxic to certain tumor cells *in vitro* and to reverse the morphology of cells transformed by the Rous sarcoma virus to a normal state.



Geldanamycin's nanomolar potency and apparent specificity for aberrant protein kinase dependent tumor cells, as well as the discovery that its primary target in mammalian cells is the ubiquitous Hsp90 protein chaperone, has stimulated interest in the development of this compound as an anti-cancer drug. However, the association of unacceptable hepatotoxicity with the administration of geldanamycin led to its withdrawal from Phase I clinical trials.

[0046] More recently, attention has focused on 17-amino derivatives of geldanamycin, in particular 17-(allylamino)-17-desmethoxygeldanamycin ("17-AAG",  $R_{17} = -NCH_2CH=CH_2$ ). This compound has reduced hepatotoxicity while maintaining useful Hsp90 binding. Certain other 17-amino derivatives of geldanamycin, 11-oxogeldanamycin, and 5,6-dihydrogeldanamycin, are disclosed in U.S. patents 4,261,989, 5,387,584 and 5,932,566, each of which is incorporated herein by reference. Treatment of cancer cells with geldanamycin or 17-AAG causes a retinoblastoma protein-dependent G1 block, mediated by down-regulation of the induction pathways for cyclin D-cyclin dependent cdk4 and cdk6 protein kinase activity. Cell cycle arrest is followed by

differentiation and apoptosis. G1 progression is unaffected by geldanamycin or 17-AAG in cells with mutated retinoblastoma protein; these cells undergo cell cycle arrest after mitosis, again followed by apoptosis.

5 [0047] The above-described mechanism of geldanamycin and 17-AAG appears to be a common mode of action among the benzoquinone ansamycins that further includes binding to Hsp90 and subsequent degradation of Hsp90-associated client proteins.

Among the most sensitive client protein targets of the benzoquinone ansamycins are the Her kinases (also known as ErbB), Raf, Met tyrosine kinase, and the steroid receptors. Hsp90 is also involved in the cellular response to stress, including heat, radiation, and  
10 toxins. Certain benzoquinone ansamycins, such as 17-AAG, have thus been studied to determine their interaction with cytotoxins that do not target Hsp90 client proteins.

[0048] U.S. Patents 6,245,759, 6,306,874 and 6,313,138, each of which is incorporated herein by reference, disclose compositions comprising certain tyrosine kinase inhibitors together with 17-AAG and methods for treating cancer with such  
15 compositions. Münster, et al., "Modulation of Hsp90 function by ansamycins sensitizes breast cancer cells to chemotherapy-induced apoptosis in an RB- and schedule-dependent manner," *Clinical Cancer Research* (2001) 7:2228-2236, discloses that 17-AAG sensitizes cells in culture to the cytotoxic effects of Paclitaxel and doxorubicin. The Münster reference further discloses that the sensitization towards paclitaxel by 17-AAG is  
20 schedule-dependent in retinoblastoma protein-producing cells due to the action of these two drugs at different stages of the cell cycle: treatment of cells with a combination of paclitaxel and 17-AAG is reported to give synergistic apoptosis, while pretreatment of cells with 17-AAG followed by treatment with paclitaxel is reported to result in abrogation of apoptosis. Treatment of cells with paclitaxel followed by treatment with  
25 17-AAG 4 hours later is reported to show a synergistic effect similar to coincident treatment.

[0049] Citri, et al., "Drug-induced ubiquitylation and degradation of ErbB receptor tyrosine kinases: implications for cancer chemotherapy," *EMBO Journal* (2002) 21:2407-2417, discloses an additive effect upon co-administration of geldanamycin and  
30 an irreversible protein kinase inhibitor, CI-1033, on growth of ErbB2-expressing cancer cells in vitro. In contrast, an antagonistic effect of CI-1033 and anti-ErbB2 antibody, Herceptin is disclosed.

[0050] Thus, while there has been a great deal of research interest in the benzoquinone ansamycins, particularly geldanamycin and 17-AAG, there remains a need for effective therapeutic regimens to treat cancer or other disease conditions characterized by undesired cellular hyperproliferation using such compounds, whether alone or in  
5 combination with other agents.

#### SUMMARY OF THE INVENTION

[0051] The present invention provides a method for treating cancer. The method involves the administration of an HSP90 inhibitor and an antimitotic, where the combined  
10 administration provides a synergistic effect.

[0052] In one aspect of the invention, a method of treating cancer is provided where a subject is treated with a dose of an HSP90 inhibitor in one step and a dose of an antimitotic in another step.

[0053] In another aspect of the invention, a method of treating cancer is provided  
15 where a subject is first treated with a dose of an HSP90 inhibitor and subsequently treated with a dose of an antimitotic.

[0054] In another aspect of the invention, a method of treating cancer is provided where a subject is first treated with a dose of an antimitotic and subsequently treated with a dose of an HSP90 inhibitor.

[0055] In another aspect of the invention, a method of treating cancer is provided  
20 where a subject is first treated with a dose of an antimitotic (e.g., docetaxel, vinblastine, vincristine, vindesine, and epothilone D). After waiting for a period of time sufficient to allow development of a substantially efficacious response of the antimitotic, a formulation comprising a synergistic dose of a benzoquinone ansamycin together with a  
25 second sub-toxic dose of the antimitotic is administered.

[0056] In another aspect of the invention, a method of treating cancer is provided where a subject is treated first with a dose of a benzoquinone ansamycin, and second, a dose of an antimitotic. After waiting for a period of time sufficient to allow development of a substantially efficacious response of the antimitotic, a formulation comprising a  
30 synergistic dose of a benzoquinone ansamycin together with a second sub-toxic dose of the antimitotic drug is administered.

[0057] In another aspect of the invention, a method for treating cancer is provided where a subject is treated with a dose of an HSP90 inhibitor in one step and a dose of an

antimitotic in another step, and where a side effect profile for the combined, administered drugs is substantially better than for the antimitotic alone.

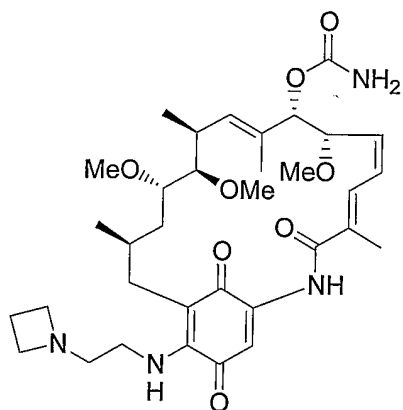
[0058] In another aspect of the invention, a method for treating breast or colorectal cancer is provided where a subject is treated with a dose of an HSP90 inhibitor in one step and a dose of an antimitotic in another step. The HSP90 inhibitor for this aspect is typically 17-AAG, while the antimitotic is usually docetaxel, vinblastine, vincristine, vindesine, or epothilone D. For the treatment of colorectal cancer, the antimitotic is typically administered before the 17-AAG; for the treatment of breast cancer, the antimitotic is typically administered after the 17-AAG. Where the antimitotic is epothilone D, it is oftentimes administered before the 17-AAG for the treatment of breast cancer.

#### Definitions

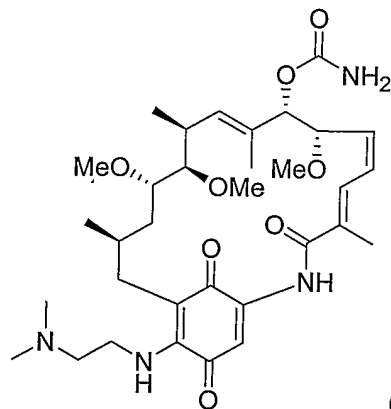
[0059] "Antimitotic" refers to a drug that inhibits or prevents mitosis or prodrugs thereof, excepting out antibiotics and enzyme inhibitors. Examples of antimitotics include, without limitation, vinblastine, vincristine, vindesine, vinorelbine, paclitaxel, docetaxel, discodermolide, epothilone D, etoposide, and teniposide.

[0060] "HSP90 inhibitor" refers to a compound that inhibits the activity of heat shock protein 90, which is a cellular protein responsible for chaperoning multiple client proteins necessary for cell signaling, proliferation and survival. One class of HSP90 inhibitors is the benzoquinone ansamycins. Examples of such compounds include, without limitation, geldanamycin and geldanamycin derivatives (*e.g.*, 17-alkylamino-17-desmethoxy-geldanamycin ("17-AAG") and 17-(2-dimethylaminoethyl)amino-17-desmethoxy-geldanamycin ("17-DMAG")). *See* Sasaki *et al.*, US 4,261,989 (1981) for synthesis of 17-AAG and Snader *et al.*, US 2004/0053909 A1 (2004) for synthesis of 17-DMAG. In addition to 17-AAG and 17-DMAG, other preferred geldanamycin derivatives are 11-*O*-methyl-17-(2-(1-azetidiny)ethyl)amino-17-demethoxygeldanamycin (A), 11-*O*-methyl-17-(2-dimethylaminoethyl)amino-17-demethoxygeldanamycin (B), and 11-*O*-methyl-17-(2-(1-pyrrolidiny)ethyl)amino-17-demethoxygeldanamycin (C), whose synthesis is described in the co-pending commonly US patent application of Tian *et al.*, serial no. 10/825,788, filed Apr. 16, 2004, and in Tian *et al.*, PCT application no. PCT/US04/11638, filed Apr. 16, 2004; the disclosures of which are incorporated herein by reference.

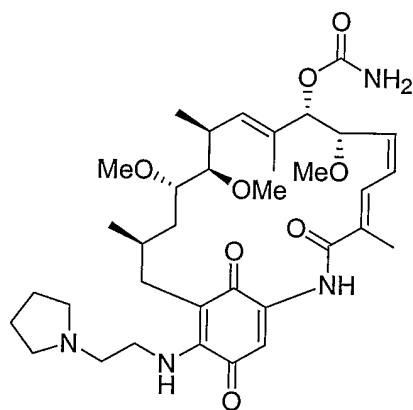
Additional preferred geldanamycin derivatives are described in Santi et al., US 2003/0114450 A1 (2003), also incorporated by reference.



(A)



(B)



(C)

[0061] "MTD" refers to maximum tolerated dose. The MTD for a compound is determined using methods and materials known in the medical and pharmacological arts, for example through dose-escalation experiments. One or more patients is first treated with a low dose of the compound, typically about 10% of the dose anticipated to be therapeutic based on results of in vitro cell culture experiments. The patients are observed for a period of time to determine the occurrence of toxicity. Toxicity is typically evidenced as the observation of one or more of the following symptoms: vomiting, diarrhea, peripheral neuropathy, ataxia, neutropenia, or elevation of liver enzymes. If no toxicity is observed, the dose is increased about 2-fold, and the patients are again observed for evidence of toxicity. This cycle is repeated until a dose producing evidence of toxicity is reached. The dose immediately preceding the onset of unacceptable toxicity is taken as the MTD.

[0062] "Side effects" refer to a number of toxicities typically seen upon treatment of a subject with an antineoplastic drug. Such toxicities include, without limitation, anemia, anorexia, bilirubin effects, dehydration, dermatology effects, diarrhea, dizziness, dyspnea, edema, fatigue, headache, hematemesis, hypokalemia, hypoxia, musculoskeletal effects, myalgia, nausea, neuro-sensory effects, pain, rash, serum glutamic oxaloacetic transaminase effects, serum glutamic pyruvic transaminase effects, stomatitis, sweating, taste effects, thrombocytopenia, voice change, and vomiting.

[0063] "Side effect grading" refers to National Cancer Institute common toxicity criteria (NCI CTC, Version 2). Grading runs from 1 to 4, with a grade of 4 representing the most serious toxicities.

#### Combination Therapy

[0064] The present invention provides a method for treating cancer. The method involves the administration of an HSP90 inhibitor and an antimitotic, where the combined administration provides a synergistic effect.

[0065] Suitable HSP90 inhibitors used in the present invention include benzoquinone ansamycins. Typically, the benzoquinone ansamycin is geldanamycin or a geldanamycin derivative. Preferably, the benzoquinone ansamycin is a geldanamycin derivative selected from a group consisting of 17-alkylamino-17-desmethoxy-geldanamycin ("17-AAG") and 17-(2-dimethylaminoethyl)amino-17-desmethoxy-geldanamycin ("17-DMAG").

[0066] Antimitotics employed in the present method include, without limitation, vinblastine, vincristine, vindesine, vinorelbine, paclitaxel, docetaxel, epothilone D, etoposide, and teniposide.

[0067] The dose of antimitotic used as a partner in combination therapy with an HSP90 inhibitor (e.g., benzoquinone ansamycin) is determined based on the maximum tolerated dose observed when the antimitotic is used as the sole therapeutic agent. In one embodiment of the invention, the dose of antimitotic when used in combination therapy with a benzoquinone ansamycin is the MTD. In other embodiments of the invention, the dose of antimitotic when used in combination therapy with a benzoquinone ansamycin is between about 1% of the MTD and the MTD, between about 5% of the MTD and the MTD, between about 5% of the MTD and 75% of the MTD, or between about 25% of the MTD and 75% of the MTD.

[0068] Use of the benzoquinone ansamycin allows for use of a lower therapeutic dose of an antimitotic, thus significantly widening the therapeutic window for treatment. In one embodiment, the therapeutic dose of antimitotic is lowered by at least about 10%. In other embodiments the therapeutic dose is lowered from about 10 % to 20%, from about 20% to 50%, from about 50% to 200%, or from about 100% to 1,000%.

[0069] For the treatment of a variety of carcinomas, the recommended intravenous dose of various antimitotics is as follows: vinblastine (for adults)—administered once/week with an initial dose of 3.7 mg/m<sup>2</sup>, with graded doses of 5.5, 7.4, 9.25 and 11.1 mg/m<sup>2</sup> at 7 day intervals; vincristine (for adults)—administered once/week with an initial dose of 0.4 to 1.4 mg/m<sup>2</sup>; vindesine—administered at a dose of 3 mg/m<sup>2</sup>; vinorelbine—30 mg/m<sup>2</sup>/week; paclitaxel—135 mg/m<sup>2</sup> given IV over 3 hours once every 3 weeks (metastatic ovarian cancer, advanced ovarian cancer, and AIDS-related Kaposi's sarcoma) and 175 mg/m<sup>2</sup> given IV over 3 hours once every 3 weeks (metastatic breast cancer); docetaxel—60-100 mg/m<sup>2</sup> given over 1 hour once every 3 weeks; epothilone D—100 mg/m<sup>2</sup> once per week; etoposide—50 to 100 mg/m<sup>2</sup> for 5 days or 100 mg/m<sup>2</sup> on alternate days for three doses (testicular cancer) and 50 to 120 mg/m<sup>2</sup> per day intravenously for 3 days or 50 mg per day orally for 21 days (small cell lung carcinoma); and, teniposide—50 mg/m<sup>2</sup> per day for 5 days to 165 mg/m<sup>2</sup> per day twice weekly (lymphoblastic leukemia).

[0070] The synergistic dose of the benzoquinone ansamycin used in combination therapy is determined based on the maximum tolerated dose observed when the benzoquinone ansamycin is used as the sole therapeutic agent. Clinical trials have determined an MTD for 17-AAG of about 40 mg/m<sup>2</sup> utilizing a daily x 5 schedule, an MTD of about 220 mg/m<sup>2</sup> utilizing a twice-weekly regimen, and an MTD of about 308 mg/m<sup>2</sup> utilizing a once-weekly regimen. In one embodiment of the invention, the dose of the benzoquinone ansamycin when used in combination therapy is the MTD. In other embodiments of the invention, the does of the benzoquinone ansamycin when used in combination therapy is between about 1% of the MTD and the MTD, between about 5% of the MTD and the MTD, between about 5% of the MTD and 75% of the MTD, or between about 25% of the MTD and 75% of the MTD.

[0071] Where the benzoquinone ansamycin is 17-AAG, and the administration of compound is weekly, its therapeutic dose is typically between 50 mg/m<sup>2</sup> and 450 mg/m<sup>2</sup>. Preferably, the dose is between 150 mg/m<sup>2</sup> and 350 mg/m<sup>2</sup>, and about 308 mg/m<sup>2</sup> is

especially preferred. Where the administration of compound is biweekly (*i.e.*, twice per week), the therapeutic dose of 17-AAG is typically between 50 mg/m<sup>2</sup> and 250 mg/m<sup>2</sup>. Preferably, the dose is between 150 mg/m<sup>2</sup> and 250 mg/m<sup>2</sup>, and about 220 mg/m<sup>2</sup> is especially preferred.

- 5 [0072] Where the present method involves the administration of 17-AAG and vinblastine, a dosage regimen involving one or two administrations of the combination per week is typical. Tables 1 and 2 below show a number of vinblastine/17-AAG dosage combinations (*i.e.*, dosage combinations 0001 to 0096).

10 **Table 1: Vinblastine/17-AAG dosage combinations.**

	30-100 mg/m <sup>2</sup> 17-AAG	100-150 mg/m <sup>2</sup> 17-AAG	150-200 mg/m <sup>2</sup> 17-AAG	200-250 mg/m <sup>2</sup> 17-AAG
0-1 mg/m <sup>2</sup> vinblastine	0001	0002	0003	0004
1-2 mg/m <sup>2</sup> vinblastine	0005	0006	0007	0008
2-3 mg/m <sup>2</sup> vinblastine	0009	0010	0011	0012
3-4 mg/m <sup>2</sup> vinblastine	0013	0014	0015	0016
4-5 mg/m <sup>2</sup> vinblastine	0017	0018	0019	0020
5-6 mg/m <sup>2</sup> vinblastine	0021	0022	0023	0024
6-7 mg/m <sup>2</sup> vinblastine	0025	0026	0027	0028
7-8 mg/m <sup>2</sup> vinblastine	0029	0030	0031	0032
8-9 mg/m <sup>2</sup> vinblastine	0033	0034	0035	0036
9-10 mg/m <sup>2</sup> vinblastine	0037	0038	0039	0040
10-11 mg/m <sup>2</sup> vinblastine	0041	0042	0043	0044
11-12 mg/m <sup>2</sup> vinblastine	0045	0046	0047	0048

**Table 2: Vinblastine/17-AAG dosage combinations continued.**

	250-300 mg/m <sup>2</sup> 17-AAG	300-350 mg/m <sup>2</sup> 17-AAG	350-400 mg/m <sup>2</sup> 17-AAG	400-450 mg/m <sup>2</sup> 17-AAG
0-1 mg/m <sup>2</sup> vinblastine	0049	0050	0051	0052
1-2 mg/m <sup>2</sup> vinblastine	0053	0054	0055	0056
2-3 mg/m <sup>2</sup> vinblastine	0057	0058	0059	0060
3-4 mg/m <sup>2</sup> vinblastine	0061	0062	0063	0064
4-5 mg/m <sup>2</sup> vinblastine	0065	0066	0067	0068
5-6 mg/m <sup>2</sup> vinblastine	0069	0070	0071	0072
6-7 mg/m <sup>2</sup> vinblastine	0073	0074	0075	0076
7-8 mg/m <sup>2</sup> vinblastine	0077	0078	0079	0080
8-9 mg/m <sup>2</sup> vinblastine	0081	0082	0083	0084
9-10 mg/m <sup>2</sup> vinblastine	0085	0086	0087	0088
10-11 mg/m <sup>2</sup> vinblastine	0089	0090	0091	0092
11-12 mg/m <sup>2</sup> vinblastine	0093	0094	0095	0096

[0073] Where the present method involves the administration of 17-AAG and vincristine, a dosage regimen involving one or two administrations of the combination per week is typical. Tables 3 and 4 below show a number of vincristine/17-AAG dosage combinations (*i.e.*, dosage combinations 0097 to 0176).

**Table 3: Vincristine/17-AAG dosage combinations.**

	<b>30-100 mg/m<sup>2</sup> 17-AAG</b>	<b>100-150 mg/m<sup>2</sup> 17-AAG</b>	<b>150-200 mg/m<sup>2</sup> 17-AAG</b>	<b>200-250 mg/m<sup>2</sup> 17-AAG</b>
<b>0-0.2 mg/m<sup>2</sup> vincristine</b>	0097	0098	0099	0100
<b>0.2-0.4 mg/m<sup>2</sup> vincristine</b>	0101	0102	0103	0104
<b>0.4-0.6 mg/m<sup>2</sup> vincristine</b>	0105	0106	0107	0108
<b>0.6-0.8 mg/m<sup>2</sup> vincristine</b>	0109	0110	0111	0112
<b>0.8-1.0 mg/m<sup>2</sup> vincristine</b>	0113	0114	0115	0116
<b>1.0-1.2 mg/m<sup>2</sup> vincristine</b>	0117	0118	0119	0120
<b>1.2-1.4 mg/m<sup>2</sup> vincristine</b>	0121	0122	0123	0124
<b>1.4-1.6 mg/m<sup>2</sup> vincristine</b>	0125	0126	0127	0128
<b>1.6-1.8 mg/m<sup>2</sup> vincristine</b>	0129	0130	0131	0132
<b>1.8-2.0 mg/m<sup>2</sup> vincristine</b>	0133	0134	0135	0136

**Table 4: Vincristine/17-AAG dosage combinations continued.**

	<b>250-300 mg/m<sup>2</sup> 17-AAG</b>	<b>300-350 mg/m<sup>2</sup> 17-AAG</b>	<b>350-400 mg/m<sup>2</sup> 17-AAG</b>	<b>400-450 mg/m<sup>2</sup> 17-AAG</b>
<b>0-0.2 mg/m<sup>2</sup> vincristine</b>	0137	0138	0139	0140
<b>0.2-0.4 mg/m<sup>2</sup> vincristine</b>	0141	0142	0143	0144
<b>0.4-0.6 mg/m<sup>2</sup> vincristine</b>	0145	0146	0147	0148
<b>0.6-0.8 mg/m<sup>2</sup> vincristine</b>	0149	0150	0151	0152
<b>0.8-1.0 mg/m<sup>2</sup> vincristine</b>	0153	0154	0155	0156
<b>1.0-1.2 mg/m<sup>2</sup> vincristine</b>	0157	0158	0159	0160
<b>1.2-1.4 mg/m<sup>2</sup> vincristine</b>	0161	0162	0163	0164
<b>1.4-1.6 mg/m<sup>2</sup> vincristine</b>	0165	0166	0167	0168
<b>1.6-1.8 mg/m<sup>2</sup> vincristine</b>	0169	0170	0171	0172
<b>1.8-2.0 mg/m<sup>2</sup> vincristine</b>	0173	0174	0175	0176

[0074] Where the present method involves the administration of 17-AAG and vindesine, a dosage regimen involving one or two administrations of the combination per week is typical. Tables 5 and 6 below show a number of vindesine/17-AAG dosage combinations (*i.e.*, dosage combinations 0177 to 0256).

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**Table 5: Vindesine/17-AAG dosage combinations.**

	30-100 mg/m <sup>2</sup> 17-AAG	100-150 mg/m <sup>2</sup> 17-AAG	150-200 mg/m <sup>2</sup> 17-AAG	200-250 mg/m <sup>2</sup> 17-AAG
0-0.3 mg/m <sup>2</sup> vindesine	0177	0178	0179	0180
0.3-0.6 mg/m <sup>2</sup> vindesine	0181	0182	0183	0184
0.6-0.9 mg/m <sup>2</sup> vindesine	0185	0186	0187	0188
0.9-1.2 mg/m <sup>2</sup> vindesine	0189	0190	0191	0192
1.2-1.5 mg/m <sup>2</sup> vindesine	0193	0194	0195	0196
1.5-1.8 mg/m <sup>2</sup> vindesine	0197	0198	0199	0200
1.8-2.1 mg/m <sup>2</sup> vindesine	0201	0202	0203	0204
2.1-2.4 mg/m <sup>2</sup> vindesine	0205	0206	0207	0208
2.4-2.7 mg/m <sup>2</sup> vindesine	0209	0210	0211	0212
2.7-3.0 mg/m <sup>2</sup> vindesine	0213	0214	0215	0216

**Table 6: Vindesine/17-AAG dosage combinations continued.**

	250-300 mg/m <sup>2</sup> 17-AAG	300-350 mg/m <sup>2</sup> 17-AAG	350-400 mg/m <sup>2</sup> 17-AAG	400-450 mg/m <sup>2</sup> 17-AAG
0-0.3 mg/m <sup>2</sup> vindesine	0217	0218	0219	0220
0.3-0.6 mg/m <sup>2</sup> vindesine	0221	0222	0223	0224
0.6-0.9 mg/m <sup>2</sup> vindesine	0225	0226	0227	0228
0.9-1.2 mg/m <sup>2</sup> vindesine	0229	0230	0231	0232
1.2-1.5 mg/m <sup>2</sup> vindesine	0233	0234	0235	0236
1.5-1.8 mg/m <sup>2</sup> vindesine	0237	0238	0239	0240
1.8-2.1 mg/m <sup>2</sup> vindesine	0241	0242	0243	0244
2.1-2.4 mg/m <sup>2</sup> vindesine	0245	0246	0247	0248
2.4-2.7 mg/m <sup>2</sup> vindesine	0249	0250	0251	0252
2.7-3.0 mg/m <sup>2</sup> vindesine	0253	0254	0255	0256

[0075] Where the present method involves the administration of 17-AAG and vinorelbine, a dosage regimen involving one or two administrations of the combination...  
 5 per week is typical. Tables 7 and 8 below show a number of vinorelbine/17-AAG dosage combinations (*i.e.*, dosage combinations 0257 to 0336).

**Table 7: Vinorelbine/17-AAG dosage combinations.**

	30-100 mg/m <sup>2</sup> 17-AAG	100-150 mg/m <sup>2</sup> 17-AAG	150-200 mg/m <sup>2</sup> 17-AAG	200-250 mg/m <sup>2</sup> 17-AAG
0-3 mg/m <sup>2</sup> vinorelbine	0257	0258	0259	0260
3-6 mg/m <sup>2</sup> vinorelbine	0261	0262	0263	0264
6-9 mg/m <sup>2</sup> vinorelbine	0265	0266	0267	0268
9-12 mg/m <sup>2</sup> vinorelbine	0269	0270	0271	0272
12-15 mg/m <sup>2</sup> vinorelbine	0273	0274	0275	0276
15-18 mg/m <sup>2</sup> vinorelbine	0277	0278	0279	0280
18-21 mg/m <sup>2</sup> vinorelbine	0281	0282	0283	0284
21-24 mg/m <sup>2</sup> vinorelbine	0285	0286	0287	0288
24-27 mg/m <sup>2</sup> vinorelbine	0289	0290	0291	0292
27-30 mg/m <sup>2</sup> vinorelbine	0293	0294	0295	0296

**Table 8: Vinorelbine/17-AAG dosage combinations continued.**

	250-300 mg/m <sup>2</sup> 17-AAG	300-350 mg/m <sup>2</sup> 17-AAG	350-400 mg/m <sup>2</sup> 17-AAG	400-450 mg/m <sup>2</sup> 17-AAG
0-3 mg/m <sup>2</sup> vinorelbine	0297	0298	0299	0300
3-6 mg/m <sup>2</sup> vinorelbine	0301	0302	0303	0304
6-9 mg/m <sup>2</sup> vinorelbine	0305	0306	0307	0308
9-12 mg/m <sup>2</sup> vinorelbine	0309	0310	0311	0312
12-15 mg/m <sup>2</sup> vinorelbine	0313	0314	0315	0316
15-18 mg/m <sup>2</sup> vinorelbine	0317	0318	0319	0320
18-21 mg/m <sup>2</sup> vinorelbine	0321	0322	0323	0324
21-24 mg/m <sup>2</sup> vinorelbine	0325	0326	0327	0328
24-27 mg/m <sup>2</sup> vinorelbine	0329	0330	0331	0332
27-30 mg/m <sup>2</sup> vinorelbine	0333	0334	0335	0336

[0076] Where the present method involves the administration of 17-AAG and paclitaxel, a dosage regimen involving one or two administrations of the combination per week or longer (*e.g.*, every 3 weeks) is typical. Tables 9 and 10 below show a number of paclitaxel/17-AAG dosage combinations (*i.e.*, dosage combinations 0337 to 0408).

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**Table 9: Paclitaxel/17-AAG dosage combinations.**

	30-100 mg/m <sup>2</sup> 17-AAG	100-150 mg/m <sup>2</sup> 17-AAG	150-200 mg/m <sup>2</sup> 17-AAG	200-250 mg/m <sup>2</sup> 17-AAG
0-20 mg/m <sup>2</sup> paclitaxel	0337	0338	0339	0340
20-40 mg/m <sup>2</sup> paclitaxel	0341	0342	0343	0344
40-60 mg/m <sup>2</sup> paclitaxel	0345	0346	0347	0348
60-80 mg/m <sup>2</sup> paclitaxel	0349	0350	0351	0352
80-100 mg/m <sup>2</sup> paclitaxel	0353	0354	0355	0356
100-120 mg/m <sup>2</sup> paclitaxel	0357	0358	0359	0360
120-140 mg/m <sup>2</sup> paclitaxel	0361	0362	0363	0364
140-160 mg/m <sup>2</sup> paclitaxel	0365	0366	0367	0368
160-180 mg/m <sup>2</sup> paclitaxel	0369	0370	0371	0372

**Table 10: Paclitaxel/17-AAG dosage combinations continued.**

	250-300 mg/m <sup>2</sup> 17-AAG	300-350 mg/m <sup>2</sup> 17-AAG	350-400 mg/m <sup>2</sup> 17-AAG	400-450 mg/m <sup>2</sup> 17-AAG
0-20 mg/m <sup>2</sup> paclitaxel	0373	0374	0375	0376
20-40 mg/m <sup>2</sup> paclitaxel	0377	0378	0379	0380
40-60 mg/m <sup>2</sup> paclitaxel	0381	0382	0383	0384
60-80 mg/m <sup>2</sup> paclitaxel	0385	0386	0387	0388
80-100 mg/m <sup>2</sup> paclitaxel	0389	0390	0391	0392
100-120 mg/m <sup>2</sup> paclitaxel	0393	0394	0395	0396
120-140 mg/m <sup>2</sup> paclitaxel	0397	0398	0399	0400
140-160 mg/m <sup>2</sup> paclitaxel	0401	0402	0403	0404
160-180 mg/m <sup>2</sup> paclitaxel	0405	0406	0407	0408

[0077] Where the present method involves the administration of 17-AAG and docetaxel, a dosage regimen involving one or two administrations of the combination per week or longer (*e.g.*, every 3 weeks) is typical. Tables 11 and 12 below show a number of docetaxel/17-AAG dosage combinations (*i.e.*, dosage combinations 0409 to 0488).

Table 11: Docetaxel/17-AAG dosage combinations.

	30-100 mg/m <sup>2</sup> 17-AAG	100-150 mg/m <sup>2</sup> 17-AAG	150-200 mg/m <sup>2</sup> 17-AAG	200-250 mg/m <sup>2</sup> 17-AAG
0-10 mg/m <sup>2</sup> docetaxel	0409	0410	0411	0412
10-20 mg/m <sup>2</sup> docetaxel	0413	0414	0415	0416
20-30 mg/m <sup>2</sup> docetaxel	0417	0418	0419	0420
30-40 mg/m <sup>2</sup> docetaxel	0421	0422	0423	0424
40-50 mg/m <sup>2</sup> docetaxel	0425	0426	0427	0428
50-60 mg/m <sup>2</sup> docetaxel	0429	0430	0431	0432
60-70 mg/m <sup>2</sup> docetaxel	0433	0434	0435	0436
70-80 mg/m <sup>2</sup> docetaxel	0437	0438	0439	0440
80-90 mg/m <sup>2</sup> docetaxel	0441	0442	0443	0444
90-100 mg/m <sup>2</sup> docetaxel	0445	0446	0447	0448

Table 12: Docetaxel/17-AAG dosage combinations continued.

	250-300 mg/m <sup>2</sup> 17-AAG	300-350 mg/m <sup>2</sup> 17-AAG	350-400 mg/m <sup>2</sup> 17-AAG	400-450 mg/m <sup>2</sup> 17-AAG
0-10 mg/m <sup>2</sup> docetaxel	0449	0450	0451	0452
10-20 mg/m <sup>2</sup> docetaxel	0453	0454	0455	0456
20-30 mg/m <sup>2</sup> docetaxel	0457	0458	0459	0460
30-40 mg/m <sup>2</sup> docetaxel	0461	0462	0463	0464
40-50 mg/m <sup>2</sup> docetaxel	0465	0466	0467	0468
50-60 mg/m <sup>2</sup> docetaxel	0469	0470	0471	0472
60-70 mg/m <sup>2</sup> docetaxel	0473	0474	0475	0476
70-80 mg/m <sup>2</sup> docetaxel	0477	0478	0479	0480
80-90 mg/m <sup>2</sup> docetaxel	0481	0482	0483	0484
90-100 mg/m <sup>2</sup> docetaxel	0485	0486	0487	0488

[0078] Where the present method involves the administration of 17-AAG and epothilone D, a dosage regimen involving one or two administrations of the combination per week or longer (*e.g.*, every 3 weeks) is typical. Tables 13 and 14 below show a number of epothilone D/17-AAG dosage combinations (*i.e.*, dosage combinations 0489 to 5 0558).

**Table 13: Epothilone D/17-AAG dosage combinations.**

	30-100 mg/m <sup>2</sup> 17-AAG	100-150 mg/m <sup>2</sup> 17-AAG	150-200 mg/m <sup>2</sup> 17-AAG	200-250 mg/m <sup>2</sup> 17-AAG
0-10 mg/m <sup>2</sup> epothilone D	0489	0490	0491	0492
10-20 mg/m <sup>2</sup> epothilone D	0493	0494	0495	0496
20-30 mg/m <sup>2</sup> epothilone D	0497	0498	0499	0500
30-40 mg/m <sup>2</sup> epothilone D	0501	0502	0503	0504
40-50 mg/m <sup>2</sup> epothilone D	0505	0506	0507	0508
50-60 mg/m <sup>2</sup> epothilone D	0509	0500	0501	0502
60-70 mg/m <sup>2</sup> epothilone D	0503	0504	0505	0506
70-80 mg/m <sup>2</sup> epothilone D	0507	0508	0509	0510
80-90 mg/m <sup>2</sup> epothilone D	0511	0512	0513	0514
90-100 mg/m <sup>2</sup> epothilone D	0515	0516	0517	0518

**Table 14: Etoposide D/17-AAG dosage combinations continued.**

	250-300 mg/m <sup>2</sup> 17-AAG	300-350 mg/m <sup>2</sup> 17-AAG	350-400 mg/m <sup>2</sup> 17-AAG	400-450 mg/m <sup>2</sup> 17-AAG
0-10 mg/m <sup>2</sup> etoposide D	0519	0520	0521	0522
10-20 mg/m <sup>2</sup> etoposide D	0523	0524	0525	0526
20-30 mg/m <sup>2</sup> etoposide D	0527	0528	0529	0530
30-40 mg/m <sup>2</sup> etoposide D	0531	0532	0533	0534
40-50 mg/m <sup>2</sup> etoposide D	0535	0536	0537	0538
50-60 mg/m <sup>2</sup> etoposide D	0539	0540	0541	0542
60-70 mg/m <sup>2</sup> etoposide D	0543	0544	0545	0546
70-80 mg/m <sup>2</sup> etoposide D	0547	0548	0549	0550
80-90 mg/m <sup>2</sup> etoposide D	0551	0552	0553	0554
90-100 mg/m <sup>2</sup> etoposide D	0555	0556	0557	0558

[0079] Where the present method involves the administration of 17-AAG and etoposide, a dosage regimen involving more than one or two administrations of the combination per week or is typical. Oftentimes the combination is administered 3, 4 or 5 times per week. Tables 15 and 16 below show a number of etoposide/17-AAG dosage combinations (*i.e.*, dosage combinations 0559 to 0654).

**Table 15: Etoposide/17-AAG dosage combinations.**

	<b>30-100 mg/m<sup>2</sup> 17-AAG</b>	<b>100-150 mg/m<sup>2</sup> 17-AAG</b>	<b>150-200 mg/m<sup>2</sup> 17-AAG</b>	<b>200-250 mg/m<sup>2</sup> 17-AAG</b>
<b>0-10 mg/m<sup>2</sup> etoposide</b>	0559	0560	0561	0562
<b>10-20 mg/m<sup>2</sup> etoposide</b>	0563	0564	0565	0566
<b>20-30 mg/m<sup>2</sup> etoposide</b>	0567	0568	0569	0570
<b>30-40 mg/m<sup>2</sup> etoposide</b>	0571	0572	0573	0574
<b>40-50 mg/m<sup>2</sup> etoposide</b>	0575	0576	0577	0578
<b>50-60 mg/m<sup>2</sup> etoposide</b>	0579	0580	0581	0582
<b>60-70 mg/m<sup>2</sup> etoposide</b>	0583	0584	0585	0586
<b>70-80 mg/m<sup>2</sup> etoposide</b>	0587	0588	0589	0590
<b>80-90 mg/m<sup>2</sup> etoposide</b>	0591	0592	0593	0594
<b>90-100 mg/m<sup>2</sup> etoposide</b>	0595	0596	0597	0598
<b>100-110 mg/m<sup>2</sup> etoposide</b>	0599	0600	0601	0602
<b>110-120 mg/m<sup>2</sup> etoposide</b>	0603	0604	0605	0606

**Table 16: Etoposide/17-AAG dosage combinations continued.**

	250-300 mg/m <sup>2</sup> 17-AAG	300-350 mg/m <sup>2</sup> 17-AAG	350-400 mg/m <sup>2</sup> 17-AAG	400-450 mg/m <sup>2</sup> 17-AAG
0-10 mg/m <sup>2</sup> etoposide	0607	0608	0609	0610
10-20 mg/m <sup>2</sup> etoposide	0611	0612	0613	0614
20-30 mg/m <sup>2</sup> etoposide	0615	0616	0617	0618
30-40 mg/m <sup>2</sup> etoposide	0619	0620	0621	0622
40-50 mg/m <sup>2</sup> etoposide	0623	0624	0625	0626
50-60 mg/m <sup>2</sup> etoposide	0627	0628	0629	0630
60-70 mg/m <sup>2</sup> etoposide	0631	0632	0633	0634
70-80 mg/m <sup>2</sup> etoposide	0635	0636	0637	0638
80-90 mg/m <sup>2</sup> etoposide	0639	0640	0641	0642
90-100 mg/m <sup>2</sup> etoposide	0643	0644	0645	0646
100-110 mg/m <sup>2</sup> etoposide	0647	0648	0649	0650
110-120 mg/m <sup>2</sup> etoposide	0651	0652	0653	0654

[0080] Where the present method involves the administration of 17-AAG and teniposide, a dosage regimen involving more than one or two administrations of the combination per week or is typical. Oftentimes the combination is administered 3, 4 or 5 times per week. Tables 17 and 18 below show a number of teniposide/17-AAG dosage combinations (*i.e.*, dosage combinations 0655 to 0742).

**Table 17: Teniposide/17-AAG dosage combinations.**

	<b>30-100 mg/m<sup>2</sup> 17-AAG</b>	<b>100-150 mg/m<sup>2</sup> 17-AAG</b>	<b>150-200 mg/m<sup>2</sup> 17-AAG</b>	<b>200-250 mg/m<sup>2</sup> 17-AAG</b>
<b>0-15 mg/m<sup>2</sup> teniposide</b>	0655	0656	0657	0658
<b>15-30 mg/m<sup>2</sup> teniposide</b>	0659	0660	0661	0662
<b>30-45 mg/m<sup>2</sup> teniposide</b>	0663	0664	0665	0666
<b>45-60 mg/m<sup>2</sup> teniposide</b>	0667	0668	0669	0670
<b>60-75 mg/m<sup>2</sup> teniposide</b>	0671	0672	0673	0674
<b>75-90 mg/m<sup>2</sup> teniposide</b>	0675	0676	0677	0678
<b>90-105 mg/m<sup>2</sup> teniposide</b>	0679	0680	0681	0682
<b>105-120 mg/m<sup>2</sup> teniposide</b>	0683	0684	0685	0686
<b>120-135 mg/m<sup>2</sup> teniposide</b>	0687	0688	0689	0690
<b>135-150 mg/m<sup>2</sup> teniposide</b>	0691	0692	0693	0694
<b>150-165 mg/m<sup>2</sup> teniposide</b>	0695	0696	0697	0698

**Table 18: Teniposide/17-AAG dosage combinations continued.**

	<b>250-300 mg/m<sup>2</sup> 17-AAG</b>	<b>300-350 mg/m<sup>2</sup> 17-AAG</b>	<b>350-400 mg/m<sup>2</sup> 17-AAG</b>	<b>400-450 mg/m<sup>2</sup> 17-AAG</b>
<b>0-15 mg/m<sup>2</sup> teniposide</b>	0699	0700	0701	0702
<b>15-30 mg/m<sup>2</sup> teniposide</b>	0703	0704	0705	0706
<b>30-45 mg/m<sup>2</sup> teniposide</b>	0707	0708	0709	0710
<b>45-60 mg/m<sup>2</sup> teniposide</b>	0711	0712	0713	0714
<b>60-75 mg/m<sup>2</sup> teniposide</b>	0715	0716	0717	0718
<b>75-90 mg/m<sup>2</sup> teniposide</b>	0719	0720	0721	0722
<b>90-105 mg/m<sup>2</sup> teniposide</b>	0723	0724	0725	0726
<b>105-120 mg/m<sup>2</sup> teniposide</b>	0727	0728	0729	0730
<b>120-135 mg/m<sup>2</sup> teniposide</b>	0731	0732	0733	0734
<b>135-150 mg/m<sup>2</sup> teniposide</b>	0735	0736	0737	0738
<b>150-165 mg/m<sup>2</sup> teniposide</b>	0739	0740	0741	0742

[0081] The method of the present invention may be carried out in at least two basic ways. A subject may first be treated with a dose on an HSP90 inhibitor and subsequently be treated with a dose of an antimetabolic. Alternatively, the subject may first be treated with a dose of an antimetabolic and subsequently be treated with a dose of an HSP90  
5 inhibitor. The appropriate dosing regimen depends on the particular antimetabolic employed.

[0082] In another aspect of the invention, a subject is first treated with a dose of an antimetabolic (e.g., docetaxel, vinblastine, vincristine, vindesine, or epothilone D). After waiting for a period of time sufficient to allow development of a substantially efficacious  
10 response of the antimetabolic, a formulation comprising a synergistic dose of a benzoquinone ansamycin together with a second sub-toxic dose of the antimetabolic is administered. In general, the appropriate period of time sufficient to allow development of a substantially efficacious response to the antimetabolic will depend upon the pharmacokinetics of the antimetabolic, and will have been determined during clinical trials  
15 of therapy using the antimetabolic alone. In one embodiment of the invention, the period of time sufficient to allow development of a substantially efficacious response to the antimetabolic is between about 1 hour and 96 hours. In another aspect of the invention, the period of time sufficient to allow development of a substantially efficacious response to the antimetabolic is between about 2 hours and 48 hours. In another embodiment of the  
20 invention, the period of time sufficient to allow development of a substantially efficacious response to the antimetabolic is between about 4 hours and 24 hours.

[0083] In another aspect of the invention, a subject is treated first with one of the above-described benzoquinone ansamycins, and second, a dose of an antimetabolic, such as, but not limited to, docetaxel, vinblastine, vincristine, vindesine and epothilone D. After  
25 waiting for a period of time sufficient to allow development of a substantially efficacious response of the antimetabolic, a formulation comprising a synergistic dose of a benzoquinone ansamycin together with a second sub-toxic dose of the antimetabolic is administered. In general, the appropriate period of time sufficient to allow development of a substantially efficacious response to the antimetabolic will depend upon the  
30 pharmacokinetics of the antimetabolic, and will have been determined during clinical trials of therapy using the antimetabolic alone. In one embodiment of the invention, the period of time sufficient to allow development of a substantially efficacious response to the antimetabolic is between about 1 hour and 96 hours. In another aspect of the invention, the

period of time sufficient to allow development of a substantially efficacious response to the antimetabolic is between about 2 hours and 48 hours. In another embodiment of the invention, the period of time sufficient to allow development of a substantially efficacious response to the antimetabolic is between about 4 hours and 24 hours.

5 [0084] As noted above, the combination of an HSP90 inhibitor and an antimetabolic allows for the use of a lower therapeutic dose of the antimetabolic for the treatment of cancer. That a lower dose of antimetabolic is used oftentimes lessens the side effects observed in a subject. The lessened side effects can be measured both in terms of incidence and severity. Severity measures are provided through a grading process  
10 delineated by the National Cancer Institute (common toxicity criteria NCI CTC, Version 2). For instance, the incidence of side effects are typically reduced 10%. Oftentimes, the incidence is reduced 20%, 30%, 40% or 50%. Furthermore, the incidence of grade 3 or 4 toxicities for more common side effects associated with antimetabolic administration (*e.g.*, anemia, anorexia, diarrhea, fatigue, nausea and vomiting) is oftentimes reduced 10%,  
15 20%, 30%, 40% or 50%.

[0085] Formulations used in the present invention may be in any suitable form, such as a solid, semisolid, or liquid form. See *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5<sup>th</sup> edition, Lippicott Williams & Wilkins (1991), incorporated herein by reference. In general the pharmaceutical preparation will contain one or more of the  
20 compounds of the present invention as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral application. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, pessaries, solutions, emulsions, suspensions, and any other form suitable for use. The carriers that  
25 can be used include water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, and other carriers suitable for use in manufacturing preparations in solid, semi-solid, or liquefied form. In addition, auxiliary stabilizing, thickening, and coloring agents and perfumes may be used. Where applicable, the compounds useful in the methods of the  
30 invention may be formulated as microcapsules and nanoparticles. General protocols are described, for example, by *Microcapsules and Nanoparticles in Medicine and Pharmacy* by Max Donbrow, ed., CRC Press (1992) and by U.S. Patent Nos. 5,510,118, 5,534,270 and 5,662,883 which are all incorporated herein by reference. By increasing the ratio of

surface area to volume, these formulations allow for the oral delivery of compounds that would not otherwise be amenable to oral delivery. The compounds useful in the methods of the invention may also be formulated using other methods that have been previously used for low solubility drugs. For example, the compounds may form emulsions with  
5 vitamin E or a PEGylated derivative thereof as described by PCT publications WO 98/30205 and WO 00/71163, each of which is incorporated herein by reference.

Typically, the compound useful in the methods of the invention is dissolved in an aqueous solution containing ethanol (preferably less than 1% w/v). Vitamin E or a PEGylated-vitamin E is added. The ethanol is then removed to form a pre-emulsion that  
10 can be formulated for intravenous or oral routes of administration. Another method involves encapsulating the compounds useful in the methods of the invention in liposomes. Methods for forming liposomes as drug delivery vehicles are well known in the art. Suitable protocols include those described by U.S. Patent Nos. 5,683,715, 5,415,869, and 5,424,073 which are incorporated herein by reference relating to another  
15 relatively low solubility cancer drug paclitaxel and by PCT Publication WO 01/10412 which is incorporated herein by reference relating to epothilone B. Of the various lipids that may be used, particularly preferred lipids for making encapsulated liposomes include phosphatidylcholine and polyethyleneglycol-derivatized distearyl phosphatidyl-ethanolamine.

20 **[0086]** Yet another method involves formulating the compounds useful in the methods of the invention using polymers such as biopolymers or biocompatible (synthetic or naturally occurring) polymers. Biocompatible polymers can be categorized as biodegradable and non-biodegradable. Biodegradable polymers degrade in vivo as a function of chemical composition, method of manufacture, and implant structure.

25 Illustrative examples of synthetic polymers include polyanhydrides, polyhydroxyacids such as polylactic acid, polyglycolic acids and copolymers thereof, polysters, polyamides, polyorthoesters and some polyphosphazenes. Illustrative examples of naturally occurring polymers include proteins and polysaccharides such as collagen, hyaluronic acid, albumin, and gelatin.

30 **[0087]** Another method involves conjugating the compounds useful in the methods of the invention to a polymer that enhances aqueous solubility. Examples of suitable polymers include polyethylene glycol, poly-(d-glutamic acid), poly-(l-glutamic acid), poly-(1-glutamic acid), poly-(d-aspartic acid), poly-(l-aspartic acid) and copolymers

thereof. Polyglutamic acids having molecular weights between about 5,000 to about 100,000 are preferred, with molecular weights between about 20,000 and 80,000 being more preferred and with molecular weights between about 30,000 and 60,000 being most preferred. The polymer is conjugated via an ester linkage to one or more hydroxyls  
5 of an inventive geldanamycin using a protocol as essentially described by U.S. Patent No. 5,977,163 which is incorporated herein by reference.

[0088] In another method, the compounds useful in the methods of the invention are conjugated to a monoclonal antibody. This method allows the targeting of the inventive compounds to specific targets. General protocols for the design and use of conjugated  
10 antibodies are described in *Monoclonal Antibody-Based Therapy of Cancer* by Michael L. Grossbard, ED. (1998), which is incorporated herein by reference.

[0089] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the subject treated and the particular mode of administration. For example, a formulation for intravenous  
15 use comprises an amount of the inventive compound ranging from about 1 mg/mL to about 25 mg/mL, preferably from about 5 mg/mL, and more preferably about 10 mg/mL. Intravenous formulations are typically diluted between about 2 fold and about 30 fold with normal saline or 5% dextrose solution prior to use.

[0090] Preferably, 17-AAG is formulated as a pharmaceutical solution formulation  
20 comprising 17-AAG in an concentration of up to 15 mg/mL dissolved in a vehicle comprising (i) a first component that is ethanol, in an amount of between about 40 and about 60 volume %; (ii) a second component that is a polyethoxylated castor oil, in an amount of between about 15 to about 50 volume %; and (iii) a third component that is selected from the group consisting of propylene glycol, PEG 300, PEG 400, glycerol, and  
25 combinations thereof, in an amount of between about 0 and about 35 volume %. The aforesaid percentages are volume/volume percentages based on the combined volumes of the first, second, and third components. The lower limit of about 0 volume % for the third component means that it is an optional component; that is, it may be absent. The pharmaceutical solution formulation is then diluted into water to prepare a diluted  
30 formulation containing up to 3 mg/mL 17-AAG, for intravenous formulation.

[0091] Preferably, the second component is Cremophor EL and the third component is propylene glycol. In an especially preferred formulation, the percentages of the first, second, and third components are 50%, 20-30%, and 20-30%, respectively.

[0092] Other formulations designed for 17-AAG are described in Tabibi et al., US 6,682,758 B1 (2004) and Ulm et al., WO 03/086381 A1 (2003); the disclosures of which are incorporated herein by reference.

[0093] The method of the present invention is used for the treatment of cancer. In one embodiment, the methods of the present invention are used to treat cancers of the head and neck, which include, but are not limited to, tumors of the nasal cavity, paranasal sinuses, nasopharynx, oral cavity, oropharynx, larynx, hypopharynx, salivary glands, and paragangliomas. In another embodiment, the compounds of the present invention are used to treat cancers of the liver and biliary tree, particularly hepatocellular carcinoma. In another embodiment, the compounds of the present invention are used to treat intestinal cancers, particularly colorectal cancer. In another embodiment, the compounds of the present invention are used to treat ovarian cancer. In another embodiment, the compounds of the present invention are used to treat small cell and non-small cell lung cancer. In another embodiment, the compounds of the present invention are used to treat breast cancer. In another embodiment, the compounds of the present invention are used to treat sarcomas, including fibrosarcoma, malignant fibrous histiocytoma, embryonal rhabdomyosarcoma, leiomyosarcoma, neuro-fibrosarcoma, osteosarcoma, synovial sarcoma, liposarcoma, and alveolar soft part sarcoma. In another embodiment, the compounds of the present invention are used to treat neoplasms of the central nervous systems, particularly brain cancer. In another embodiment, the compounds of the present invention are used to treat lymphomas which include Hodgkin's lymphoma, lymphoplasmacytoid lymphoma, follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, mantle cell lymphoma, B-lineage large cell lymphoma, Burkitt's lymphoma, and T-cell anaplastic large cell lymphoma.

#### Examples

[0094] The following Examples are provided to illustrate certain aspects of the present invention and to aid those of skill in the art in practicing the invention.

#### Materials and Methods

##### *Cell line and reagents*

[0095] Human colon adenocarcinoma cell line, DLD-1, and human breast adenocarcinoma cell line, SKBr-3, were obtained from American Type Culture Collection

(manassas, VA). DLD-1 cells were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum, and SKBr-3 cells were cultured in McCoy's 5a medium supplemented with 10 % fetal bovine serum. 17-DMAG and 17-AAG were obtained using published procedures. Other cytotoxic agents were purchased commercially from  
5 suppliers such as Sigma Chemical Co. (St. Louis, MO) and Sequoia Research Products (Oxford, UK).

*Cell viability assay and combination effect analysis*

[0096] Cells were seeded in duplicate in 96-well microtiter plates at a density of  
10 5,000 cells per well and allowed to attach overnight. Cells were treated with 17-AAG or 17-DMAG and the corresponding antimetabolic at varying concentrations, ranging from 0.5 picomolar ("pM") to 50 micromolar ("µM"), for 3 days. Cell viability was determined using the MTS assay (Promega). For the drug combination assay, cells were seeded in duplicate in 96-well plates (5,000 cells/well). After an overnight incubation, cells were  
15 treated with drug alone or a combination and the IC<sub>50</sub> value (the concentration of drug required to inhibit cell growth by 50%) was determined. Based on the IC<sub>50</sub> values of each individual drug, combined drug treatment was designed at constant ratios of two drugs, *i.e.*, equivalent to the ratio of their IC<sub>50</sub>. Two treatment schedules were used: In one schedule, the cells were exposed to 24 hours of 17-AAG or 17-DMAG. The drug was  
20 then added to the cells and incubated for 48 hours. In another schedule, cells were exposed to the drug alone for 24 hours followed by addition of 17-AAG or 17-DMAG for 48 hours. Cell viability was determined by the MTS assay.

[0097] Synergism, additivity or antagonism was determined by median effect analysis using the combination index (CI) calculated using CalcuSyn (Biosoft, Cambridge, UK).  
25 The combination index is defined as follows:

$$CI = [D]_1/[D_x]_1 + [D]_2/[D_x]_2$$

The quantities [D]<sub>1</sub> and [D]<sub>2</sub> represent the concentrations of the first and second drug,  
30 respectively, that in combination provide a response of x % in the assay. The quantities [D<sub>x</sub>]<sub>1</sub> and [D<sub>x</sub>]<sub>2</sub> represent the concentrations of the first and second drug, respectively, that when used alone provide a response of x % in the assay. Values of CI < 1, CI = 1, and CI

> 1 indicated drug-drug synergism, additivity, and antagonism respectively (Chou and Talalay 1984). The “enhancing” effect of two drugs can also be determined.

### Results

#### 5 *17-AAG combination in DLD-1 cells*

[0098] The following table provides CI values for combinations of 17-AAG and the antimitotics docetaxel, vinblastine, vincristine, vindesine, and epothilone D in a DLD-1 cell assay. “Pre-administration” refers to the administration of 17-AAG to the cells before the administration of antimitotic; “post-administration” refers to the administration of 17-AAG to the cells after the administration of antimitotic.

**Table 5: CI values for combinations in DLD-1 cells (human colorectal cancer cells).**

Antimitotic	17-AAG Pre-Administration	17-AAG Post-Administration
Docetaxel	0.79 ± 0.15	0.29 ± 0.12
Vinblastine	0.92 ± 0.3	0.38 ± 0.11
Vincristine	0.96 ± 0.3	0.42 ± 0.08
Vindesine	0.91 ± 0.41	0.68 ± 0.08
Epothilone D	0.84 ± 0.06	0.61 ± 0.12

#### *17-AAG combination in SKSBr-3 cells*

15 [0099] The following table provides CI values for combinations of 17-AAG and the antimitotics docetaxel, vinblastine, vincristine, and epothilone D in an SKBr-3 cell assay.

**Table 6: CI values for combinations in SKBr cells (human breast cancer cells).**

Antimitotic	17-AAG Pre-Administration	17-AAG Post-Administration
Docetaxel	0.53 ± 0.11	0.59 ± 0.26
Vinblastine	0.39 ± 0.03	0.68 ± 0.41
Vincristine	0.67 ± 0.37	0.99 ± 0.73
Epothilone D	0.72 ± 0.07	0.58 ± 0.009

#### 20 *Additional Observations*

[00100] Additional analysis indicated that both 17-AAG and 17-DMAG reduced the expression of ErbB2 protein in SKBr3 and glioma cells. This observation, taken in combination with the results reported above, indicates that combinations of 17-AAG or 17-DMAG with any of the antimitotics above that are known to be useful to treat diseases

characterized by elevated ErbB2 protein expression (*i.e.*, levels of expressions of ErbB2 protein greater than those found in healthy cells).

Claims

1. A method for treating breast cancer in a patient, wherein the method comprises administering an HSP90 inhibitor and an antimitotic to the patient.

5

2. The method of claim 1, wherein the HSP90 inhibitor is administered to the patient before the antimitotic.

3. The method of claim 1, wherein the HSP90 inhibitor is administered to the patient after the antimitotic.

10

4. The method of claim 2, wherein the HSP90 inhibitor is geldanamycin or a geldanamycin derivative.

15

5. The method of claim 3, wherein the HSP90 inhibitor is geldanamycin or a geldanamycin derivative.

6. The method of claim 4, wherein the HSP90 inhibitor is a geldanamycin derivative, and wherein the derivative is 17-AAG.

20

7. The method of claim 5, wherein the HSP 90 inhibitor is a geldanamycin derivative, and wherein the derivative is 17-AAG.

8. The method of claim 6, wherein the antimitotic is docetaxel, vinblastine, or epothilone D.

25

9. The method of claim 7, wherein the antimitotic is epothilone D.

10. A method for treating colorectal cancer in a patient, wherein the method comprises administering an HSP90 inhibitor and an antimitotic to the patient.

30

11. The method of claim 10, wherein the HSP90 inhibitor is administered to the patient after the antimitotic.

12. The method of claim 10, wherein the HSP90 inhibitor is administered to the patient before the antimitotic.

5 13. The method of claim 11, wherein the HSP90 inhibitor is geldanamycin or a geldanamycin derivative.

14. The method of claim 12, wherein the HSP90 inhibitor is geldanamycin or a geldanamycin derivative.

10

15. The method of claim 13, wherein the HSP90 inhibitor is a geldanamycin derivative, and wherein the derivative is 17-AAG.

16. The method of claim 14, wherein the HSP90 inhibitor is a geldanamycin derivative, and wherein the derivative is 17-AAG.

15

17. The method of claim 1, wherein the HSP90 inhibitor is 17-AAG, and wherein the administration of 17-AAG and the enzyme inhibitor is performed once per week.

20

18. The method of claim 1, wherein the HSP90 inhibitor is 17-AAG, and wherein the administration of 17-AAG and the enzyme inhibitor is performed twice per week.

25 19. The method of claim 10, wherein the HSP90 inhibitor is 17-AAG, and wherein the administration of 17-AAG and the enzyme inhibitor is performed once per week.

30 20. The method of claim 10, wherein the HSP90 inhibitor is 17-AAG, and wherein the administration of 17-AAG and the enzyme inhibitor is performed twice per week.

21. The method of claim 17, wherein the therapeutic dose of 17-AAG is between 50 mg/m<sup>2</sup> and 450 mg/m<sup>2</sup>.

22. The method of claim 18, wherein the therapeutic dose of 17-AAG is  
5 between 50 mg/m<sup>2</sup> and 250 mg/m<sup>2</sup>.

23. The method of claim 19, wherein the therapeutic dose of 17-AAG is between 50 mg/m<sup>2</sup> and 450 mg/m<sup>2</sup>.

10 24. The method of claim 20, wherein the therapeutic dose of 17-AAG is between 50 mg/m<sup>2</sup> and 250 mg/m<sup>2</sup>.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/16888

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC(7) : A61K 31/535  
 US CL : 514/234.5  
 According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
 Minimum documentation searched (classification system followed by classification symbols)  
 U.S. : 514/234.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
 none

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 2003/0114450 A1 (SANTI et al.) 19 June 2003 (19.06.2003), see entire document, especially [0105]; [0126].	1-24
X, E	US 2004/0110662 A1 (ROSEN et al.) 10 June 2004 (10.06.2004), see entire document, especially the abstract; [0019], [0024], [0028], [0061], [0084], [0088].	1-9, 17-18, 21-22
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Y,E		10-16, 19-20, 23-24

Further documents are listed in the continuation of Box C.  See patent family annex. 3

* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	
"P"	document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search: 13 October 2004 (13.10.2004)  
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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US04/16888

Continuation of B. FIELDS SEARCHED Item 3:

EAST: geldanamycin, 17-AAG, colorectal, colon, breast, mammary, cancer, tumor, tumour, neoplasm, carcinoma, adenocarcinoma, vinblastine, vincristine, vindesine, vinorelbine, paclitaxel, docetaxel, epothilone D, etoposide, teniposide