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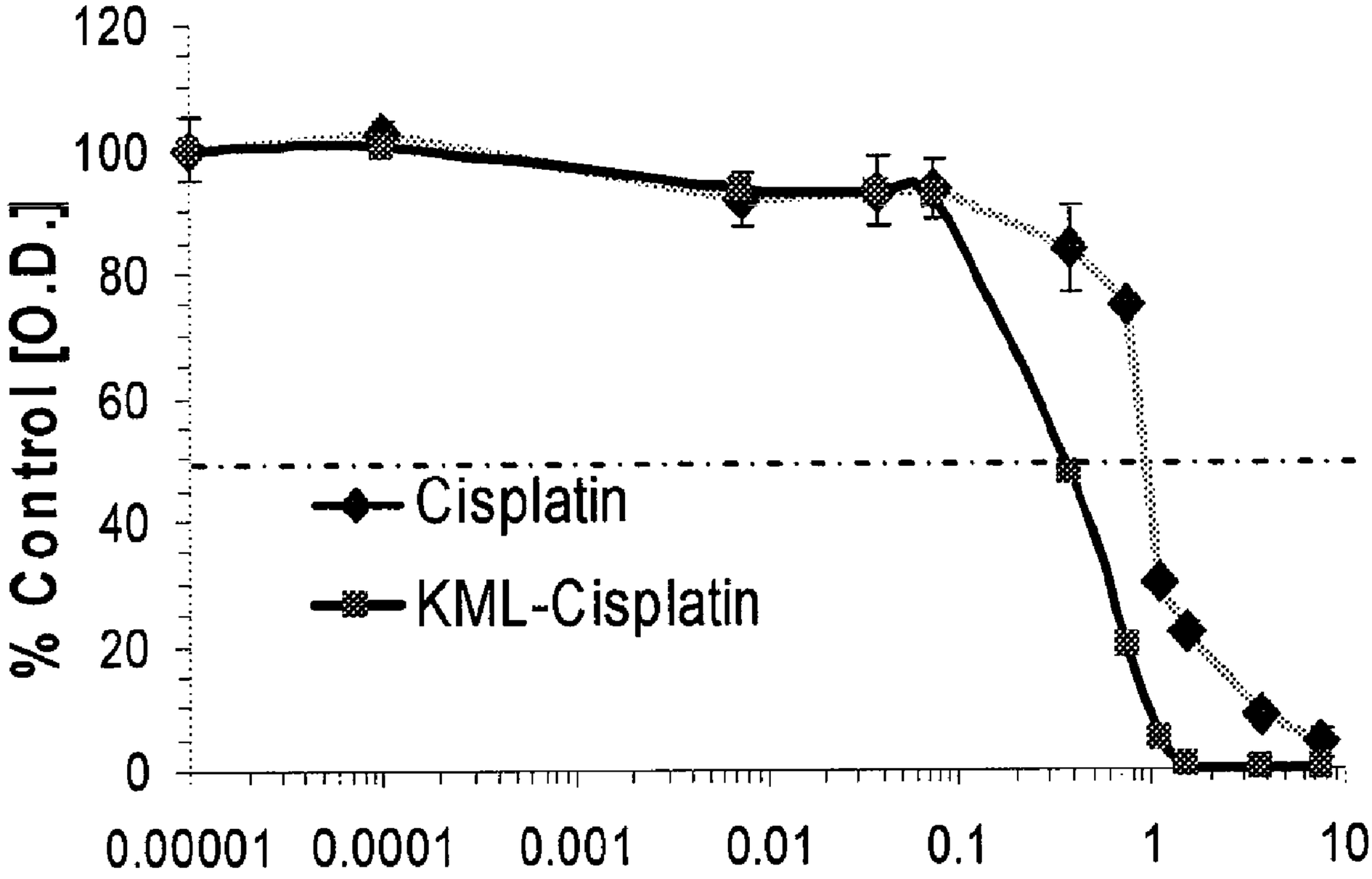
(54) **Titre : METHODE ET COMPOSITIONS POUR LE TRAITEMENT DU CANCER**
(54) **Title: METHOD AND COMPOSITIONS FOR TREATMENT OF CANCER**



(57) **Abrégé/Abstract:**
The present invention relates to a method of treating cancer in a subject in need thereof, by administering to the subject a combination of sodium meta arsenite and/or arsenic trioxide and a cytotoxic anticancer agent, such as cisplatin, adriamycin, docetaxel or paclitaxel. The arsenic compound(s) and cytotoxic anti-cancer agent may be administered together in a composition or separately as a combination therapy.

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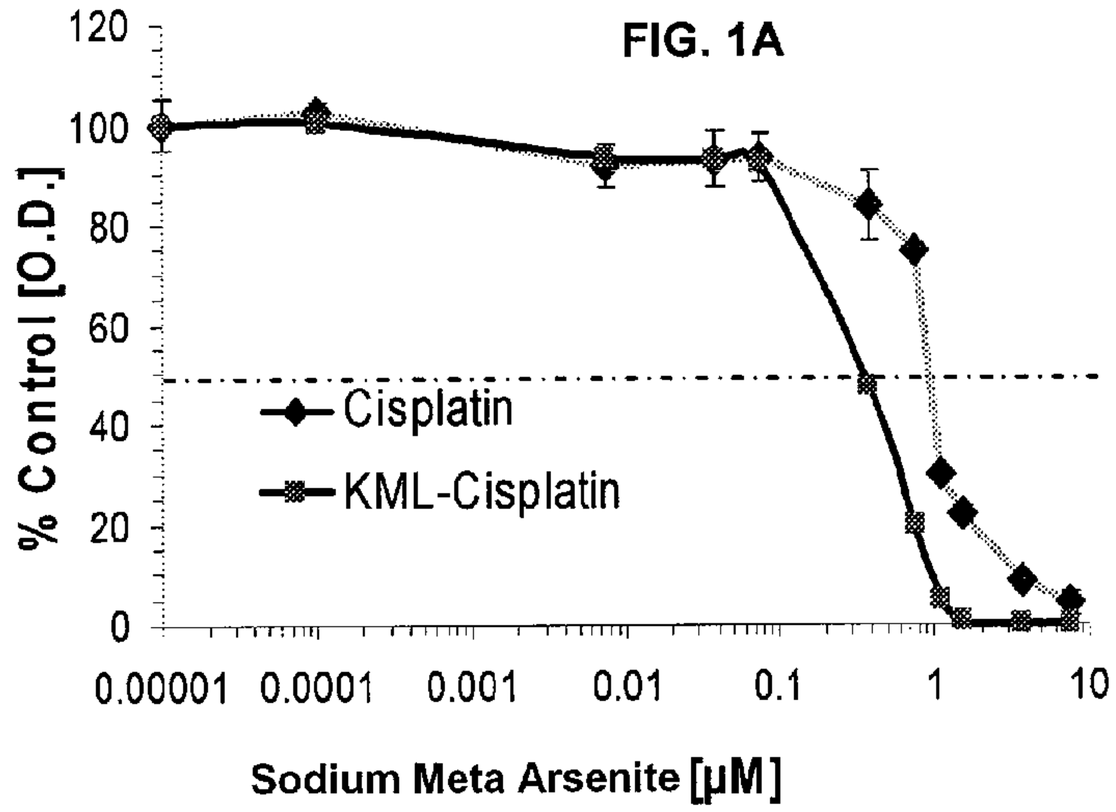
FIG. 1A



(57) Abstract: The present invention relates to a method of treating cancer in a subject in need thereof, by administering to the subject a combination of sodium meta arsenite and/or arsenic trioxide and a cytotoxic anticancer agent, such as cisplatin, adriamycin, docetaxel or paclitaxel. The arsenic compound(s) and cytotoxic anti-cancer agent may be administered together in a composition or separately as a combination therapy.

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METHOD AND COMPOSITIONS FOR TREATMENT OF CANCER

DESCRIPTION OF THE INVENTION

Field of the Invention

[0002] The present invention relates generally to a combination treatment exhibiting synergistic inhibition of the growth and/or proliferation of cancer. More particularly, the invention relates to a kits, compositions and methods including a combination therapy in which sodium meta arsenite or arsenic trioxide and a second cytotoxic agent that inhibits telomeres, such as cisplatin or a taxane are used for treatment of cancer including solid tumors and leukemia.

Background of the Invention

[0003] Chemotherapy, the systemic administration of antineoplastic agents that travel throughout the body *via* the blood circulatory system, along with and often in conjunction with surgery and/or radiation treatment, has for years been widely utilized in the treatment of a wide variety of cancers.

[0004] Today, there are a variety of antineoplastic agents that have successfully been used in the treatment of cancer. However, the search continues for more efficacious and less toxic agents.

[0005] For example, the treatment of cancer patients with platinum coordination complex antineoplastic agents, such as cis-diamminedichloroplatinum (II) (cisplatin) has increased substantially in the last decade. Cisplatin is an antineoplastic agent that has proved useful in the treatment of multiple malignancies including testicular cancer, ovarian cancer, bladder, head and neck and some lung cancers. In particular, cisplatin has been shown to be especially efficacious in the treatment of cancer cells that have long telomeres. Cisplatin is classified as a pro-drug, and once activated, it interacts with nucleophilic sites in DNA, creating predominantly purine-purine intrastrand cross-links. This genotoxic stress activates signal transduction pathways, which in most cells leads to DNA synthesis arrest and programmed cell death. Unfortunately, the initial success of cisplatin chemotherapy is often short-lived, as recurrence of the cancer occurs in many cases. The potential of the platinum-based chemotherapeutics is limited by several factors, including dangerous side effects, limited solubility, and intrinsic or acquired resistance. Thus, new therapies are needed for the treatment of cancer patients.

[0006] Like cisplatin, the anti-cancer agents, adriamycin and taxanes, such as paclitaxel, larotaxel, orataxel, tesetaxel and docetaxel, are believed to bind to telomeres or interfere with telomerases. These anti-cancer agents are routinely used to treat bladder, prostate, lung, breast, ovarian and other solid tumors as well as leukemias. However, like cisplatin, their efficacy is often limited by extrinsic factors.

[0007] The use of arsenic compounds as therapeutic agents is currently experiencing a revival, particularly in the field of oncology. Studies have shown that certain arsenic compounds are effective

against malignancies such as acute promyelocytic leukaemia (APL) (arsenic trioxide) or urogenital cancer (sodium meta arsenite). See Shen, Z.X. et al. *Blood* 1997;89: 3354-3360; Soignet, S.L. et al. *N. Engl. J. Med.* 1998; 339: 1341-1348; WO2006121280 A1. Clinical trials of the use of arsenic trioxide in the treatment of APL patients are being conducted in the US and the mechanism(s) of action of various arsenic compounds is being studied to enable rational use of inorganic arsenic. See Chou, W.C. et al. *J. Clin. Invest.* 2001; 108: 1541-1547; Senior K. *Drug Discovery Today* 2002; 7: 156-157.

[0008] In these clinical trials, it has been reported that arsenic trioxide exerts antitumor effects by activating apoptosis, by induction of reactive oxygen species and by degradation of PML-RARa fusion protein (Chou et al.). Most recently, its efficacy has been linked to the inhibition of the transcription of the reverse transcriptase subunit of the human telomerase gene (hTERT) and subsequently induction of telomere shortening as well as of chromosomal instability (Chou et al. and Senior, *supra*).

[0009] Similarly, studies have shown that sodium meta arsenite inactivates transcription of the hTERT gene and is capable of shortening telomeres in human cancer cells, indicating that it is a telomere poison. However, sodium meta arsenite is most effective in the treatment of cancers having short telomeres.

[0010] Thus, there remains a need for an improved method and compositions for the treatment of cancer, including solid tumors, leukemias and metastasis.

SUMMARY OF THE INVENTION

[0011] Effective treatment of cancer and/or prevention of metastasis is achieved by administration of sodium meta arsenite ($NaAsO_2$) or arsenic trioxide in combination with cisplatin, adriamycin and/or or a taxane, such as docetaxel, larotaxel, orataxel, tesetaxel or paclitexel. The present invention relates to compositions, kits and methods (e.g. combination therapies) comprising sodium meta arsenite and/or arsenic trioxide and cisplatin, adriamycin, or

a taxane, such as paclitaxel, larotaxel, orataxel, tesetaxel or docetaxel, or combinations thereof. The compositions, kits and methods of the present invention can be used for the prevention, intervention, and/or treatment of a neoplastic disease disclosed herein.

[0012] In one aspect of the invention there is provided a method for treating solid tumors, leukemia or metastasis in a patient comprising administering to the patient a therapeutic amount of an arsenic compound selected from sodium meta arsenite and arsenic trioxide and a therapeutic amount of cisplatin. In one embodiment, the arsenic compound is sodium meta arsenite, which may be administered orally, while cisplatin is administered *via* infusion. In other embodiments, the cancer being treated is lung cancer or breast cancer or ovarian cancer.

[0013] In certain embodiments of the invention, sodium meta arsenite and/or arsenic trioxide is administered in a therapeutically effective amount to a patient who is undergoing anti-cancer treatment with cisplatin, adriamycin, paclitaxel, docetaxel or a combination thereof.

[0014] In another aspect of the invention there is provided a kit containing a plurality of therapeutically effective dosages of sodium meta arsenite and/or arsenic trioxide and cisplatin, adriamycin, and/or taxane, *e.g.*, larotaxel, orataxel, tesetaxel, docetaxel or paclitaxel. In one embodiment, the kit contains oral dosage forms of sodium meta arsenite and a parenteral formulation of cisplatin and/or a taxane such as larotaxel, orataxel, tesetaxel, paclitaxel or docetaxel. In another embodiment the sodium meta arsenite and/or arsenic trioxide and cisplatin, adriamycin, larotaxel, orataxel, tesetaxel, docetaxel and/or paclitaxel are formulated for administration *via* infusion.

[0015] In yet another aspect of the invention, compositions are provided, which comprise a therapeutically effective amount of sodium meta arsenite or arsenic trioxide in admixture with a therapeutically effective amount of cisplatin.

[0015a] An anti-cancer agent comprising:

- a first composition comprising sodium meta arsenite and a pharmaceutically acceptable carrier and

- a second composition comprising cisplatin, docetaxel or paclitaxel and a pharmaceutically acceptable carrier.

[0015b] Use of the anti-cancer agent as defined herein for treatment of lung cancer.

[0015c] Use of the anti-cancer agent as defined herein for treatment of cancer cells containing chromosomes having telomeres of from 4 to 6Kb.

[0015d] Use of the anti-cancer agent as defined herein for treatment of prostate cancer.

[0015e] Use of the anti-cancer agent as defined herein for the preparation of a medicament for the treatment of lung cancer.

[0015f] Use of the anti-cancer agent as defined herein for the preparation of a medicament for the treatment of cancer cells containing chromosomes having telomeres of from 4 to 6Kb.

[0015g] Use of the anti-cancer agent as defined herein for the preparation of a medicament for the treatment of prostate cancer.

[0016] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figure 1A is a graph of the growth curve for single agent cisplatin (diamonds) and the simultaneous combination of cisplatin with sodium meta arsenite (squares) in A549 cells; results are from MTT proliferation assays.

[0018] Figure 1B is the Combination Index (CI) effect blot (Fa = fraction effect) for the combination of sodium meta arsenite and cisplatin in A549 cells.

[0019] Figure 1C is the Combination Index (CI) effect blot (Fa = fraction effect) for the combination of sodium meta arsenite and cisplatin in H460 cells. CI< 1 demonstrates synergy. C = 1 is additive; C>1 is antagonistic.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Use of a kit, composition or method (*e.g.*, combination therapy) of the invention results in a synergetic anti-cancer effect to achieve maximum therapeutic benefit, and can improve tolerance to the therapy with a reduced risk of side effects that often result from use of higher doses or longer term monotherapies (*i.e.*, therapies with each compound alone). Therefore, the compositions, kits and methods of the invention may enable the use of lower doses of each compound (*e.g.*, lower doses of the arsenic compound or cisplatin) with reduced adverse effects of each compound (*e.g.*, reduced side effects of arsenic compounds or cancer medicaments such as cisplatin). Suboptimal dosages can provide increased safety margins, and can also reduce the costs of drug(s) necessary to achieve prophylaxis and therapy. A synergistic

treatment utilizing a combination of the arsenic compound(s) and cisplatin, adriamycin, docetaxel and/or paclitaxel or other taxane can also provide increased convenience and may result in enhanced compliance. Advantages of a combination therapy can additionally include higher stability towards degradation and metabolism, longer duration of action, and/or longer duration of action or effectiveness at particularly low doses.

[0021] In certain aspects of the invention, the invention relates to a kit, in particular a kit containing pharmaceutical compositions, comprising sodium meta arsenite and/or arsenic trioxide and cisplatin or other cytostoxic anti-cancer agent, such as adriamycin, docetaxel or paclitaxel, as well as combinations of the cytotoxic anti-cancer agents, optionally in combination with pharmaceutically acceptable carriers, excipients, or vehicles.

[0022] The present methods for treating cancer comprise administering to a mammal in need of such treatment an effective amount of the arsenic compound(s) in combination with cisplatin or another cytotoxic anti-cancer agent that inhibits or interferes with telomeres, such as a taxane. The arsenic compound or combination of arsenic compounds may be administered either prior to, after or concurrently with administration of cisplatin or other such cytotoxic anti-cancer agent. For example, a daily dosage of the arsenic compound can be administered for one to ten days, followed by a dosage regimen of the cytotoxic agent(s) of one to ten days, or longer as necessary. Alternatively, the cytotoxic agent(s) may be delivered prior to the arsenic compound(s). Also, both the arsenic compound(s) and cytotoxic agent(s) may be administered to the patient concurrently, although not necessarily at the same time. The dosing regimen can readily be ascertained by the treating physician based on such factors as dosages of each of the drugs being administered, type and stage of the cancer, patient health, and the like.

[0023] When the arsenic compound is sodium meta arsenite, it may be administered in any form, *e.g.*, orally, *via* infusion, rectally, intraperitoneally, etc. When arsenic trioxide is included in the treatment, it may be administered *via* infusion in some embodiments of the invention, but any acceptable administration route may be used. Similarly, cisplatin or other cytotoxic anti-cancer agent, e.g., taxane, is generally administered *via* infusion, but may be administered *via* any acceptable route known in the art.

[0024] The invention provides improved methods and products for the treatment of subjects having cancer or at risk of developing cancer or metastasis of a primary tumor. The invention is based, in part, on the finding that when sodium meta arsenite ($NaAsO_2$) and/or arsenic trioxide is used in conjunction with cisplatin or other teleomere inhibiting cytotoxic anti-cancer agent, such as adriamycin or taxane, such as docetaxel and/or paclitaxel, some unexpected and improved results are observed that indicate synergy between the arsenic and non-arsenic anticancer agents. For instance, the efficacy of the combination therapy is profoundly improved in cancer patients whose tumors have longer telomeres over the use of either of the anticancer agents alone. Also, the toxicity of the combination therapy may be greatly reduced in cancer patients in comparison to the use of either of the anticancer agents alone.

[0025] The invention also encompasses use of a telomerase inhibitor other than cisplatin in combination with either sodium meta arsenite or arsenic trioxide. For example, it is contemplated that the combination of one of these arsenic compounds with adriamycin, and/or a toxane such as docetaxel or paclitaxel, which are known to synergize with other telomerase inhibitors or a telomerase binding peptides or small molecules that block and inhibit telomere repair may be used in the kits, compositions and methods of the invention. The skilled practitioner can readily determine the dosage amount, formulation and regimen for

administration of these telomerase inhibitors based on their known usage in combination with other anti-cancer drugs or usage as single agent anti-cancer therapeutics.

[0026] According to the present invention, the combination of the arsenic compound(s) and cisplatin and/or other cytotoxic anti-cancer agent, e.g., adriamycin, taxane, *e.g.*, docetaxel and/or paclitaxel, enables the effective treatment of cancers that may not be successfully treatable with either drug alone. For example, cisplatin is known to be an effective treatment for some lung cancers, especially those with long telomeres, while sodium meat arsenite is more effective in the treatment of cancers with short telomeres, *e.g.*, prostate cancer. However, the combination of cisplatin and sodium meta arsenite is surprisingly significantly more effective in the treatment of tumor cells with long telomeres, *i.e.*, certain lung cancers, than cisplatin alone. Accordingly, the present invention provides compositions and methods for the synergistic treatment of a variety of solid tumors and/or malignant diseases or conditions, including, but not limited to, the following: carcinoma including that of the bladder (including accelerated and metastatic bladder cancer), breast, cervical, colon (including colorectal cancer), kidney, liver, lung (including small and non-small cell lung cancer and lung adenocarcinoma), ovary, prostate, testes, genitourinary tract, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, cervix, thyroid, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, histiocytic lymphoma, and Burketts lymphoma; hematopoietic tumors of myeloid lineage including acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, and promyelocytic leukemia; tumors of the central and peripheral nervous system including astrocytoma,

neuroblastoma, glioma, and schwannomas; tumors of mesenchymal origin including fibrosarcoma, liposarcoma, rhabdomyosarcoma, and osteosarcoma; and other tumors including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, and teratocarcinoma.

[0027] In certain embodiments of the invention cisplatin, adriamycin, and/or taxane, such as larotaxel, orataxel, tesetaxel, docetaxel and/or paclitaxel is administered in the treatment of a patient who is being subjected to a treatment regime of sodium meta arsenite and/or arsenic trioxide. In certain embodiments, the patient undergoing such treatment has lung cancer or breast cancer or ovarian cancer. In other embodiments, cisplatin is administered in the treatment of a patient who is being subjected to a treatment regime of sodium meta arsenite.

[0028] The present invention further provides compositions, kits and methods for the treatment of a variety of solid tumors and leukemias including, but not limited to, those tumors listed in Table 1.

Table 1.

Fibrosarcoma	colon cancer	adenocarcinoma
myxosarcoma	colorectal cancer	sweat gland carcinoma
Liposarcoma	kidney cancer	sebaceous gland carcinoma
chondrosarcoma	pancreatic cancer	papillary carcinoma
osteogenic sarcoma	bone cancer	papillary adenocarcinomas
Chordoma	breast cancer	cystadenocarcinoma
angiosarcoma	ovarian cancer	papillary adenocarcinomas
endotheliosarcoma	prostate cancer	cystadenocarcinoma
lymphangiosarcoma	esophogeal cancer	medullary carcinoma
lymphangioendotheliosarcoma	stomach cancer	bronchogenic carcinoma
Synovioma	oral cancer	renal cell carcinoma
Mesothelioma	nasal cancer	hepatoma
Ewing's tumor	throat cancer	bile duct carcinoma
leiomyosarcoma	squamous cell carcinoma	choriocarcinoma
rhabdomyosarcoma	basal cell carcinoma	seminoma

embryonal carcinoma	lung cancer	craniopharyngioma
Wilms' tumor	epithelial carcinoma	ependymoma
Cervical cancer	Glioma	pinealoma
uterine cancer	Glioblastoma multiforme	hemangioblastoma
testicular cancer	Astrocytoma	acoustic neuroma
small cell lung carcinoma	medulloblastoma	oligodendroglioma
bladder carcinoma	skin cancer	meningioma
retinoblastoma	Melanoma	bronchogenic carcinoma
Medullary carcinoma	neuroblastoma	

[0029] In certain embodiments, the present invention provides compositions, kits and methods for the treatment of lung cancer. Most lung cancers exhibit striking chromosomal abnormalities and overexpression of certain oncogenes. Lung cancer can be histologically subclassified into squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma (non-small cell carcinoma), carcinoid tumor, mesothelioma, etc.

[0030] In certain embodiments of the invention, the kits and compositions may further comprise another therapeutic agent useful for the treatment of a particular cancer or tumor. For example the kits, compositions and methods may include one or more optional treatment agents, such as immunotherapeutic agents, cancer vaccines, biological response modifiers (*e.g.*, cytokines and hemopoietic growth factors), or hormone therapies (*e.g.*, adrenocorticosteroids, androgens, anti-androgens, estrogens, anti-estrogens, progestins, aromatase inhibitor, gonadotropin-releasing hormone agonists, somatostatin analog; and the like.

[0031] In still another embodiment, the optional treatment agent is a hormone, such as, when appropriate, an estrogen therapy e.g., diethylstilbestrol and ethinyl estradiol, anti-estrogen therapy *e.g.*, tamoxifen, progestin therapy *e.g.*, medroxyprogesterone and megestrol acetate, androgen blockade *e.g.*, anti-androgens such as flutamide, adrenocorticosteroids including adrenal steroids, synthetic glucocorticoid therapy *e.g.*, prednisone, methylprednisone, and

dexamethasone, androgens e.g., fluoxymesterone, synthetic testosterone analogs, aromatase inhibitor *e.g.*, aminoglutethimide, gonadotropin-releasing hormone agonists *e.g.*, leuprolide, somatostatin analogs *e.g.*, octreotide. In certain embodiments, the method further comprises administering interferon-α to the subject.

[0032] As used herein, the term "pharmaceutical composition" refers to either a mixture or combination of an arsenic compound selected from arsenic trioxide, sodium meta arsenite and combinations thereof, and cisplatin, adriamycin, docetaxel, paclitaxel or combinations thereof or each of the selected compounds alone. A pharmaceutical composition can include other chemical components, such as physiologically/pharmaceutically acceptable carriers and excipients.

[0033] As used herein, “treating” or “treatment” refers to the administration of two or more agents (*i.e.*, an arsenic compound or arsenic compounds and cisplatin, adriamycin, docetaxel, paclitaxel, or combination thereof or other cytotoxic anti-cancer agent) to a subject having or at risk of developing cancer or metastasis. “Inhibition of the growth of tumor cells” refers to the inhibition of the growth of tumor cells present in the patient. Such treatment may also lead to the regression of tumor growth, *i.e.*, the decrease in size of a measurable tumor. In some embodiments of the invention, such treatment leads to the complete regression of the tumor.

[0034] The term "prevention" includes either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk, *e.g.*, metastasis. Also intended to be encompassed by this definition is the prevention of initiation for malignant cells or to arrest or reverse the progression of premalignant

cells to malignant cells. This includes prophylactic treatment of those at risk of developing the neoplasia.

[0035] As used herein, the term "synergistic result" or "synergy" refers to a therapeutic effect against a particular cancer such that when administered in combination, the arsenic compound and cisplatin or other cytotoxic agent of the invention produce results that are significantly better than the optimal efficacy obtained with either single agent alone in the treatment of the cancer.

[0036] As used herein, “administration” or “administer” or “administering” refers to dispensing, applying, or tendering two or more agents (for example sodium meta arsenite and/or arsenic trioxide and cisplatin, adriamycin and/or taxane, *e.g.*, paclitaxel or docetaxel) to a subject. Administration can be performed using any of a number of methods known in the art. For example, "administering" as used herein is meant *via* infusion (intravenous administration (i.v.)), parenteral and/or oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration. In the use of the subject invention, sodium meta arsenite, for example, can be administered simultaneously with, for example, cisplatin, or the compounds can be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according to, *interalia*, the particular formulation of arsenic compound being utilized; the particular formulation of ther cytotoxic anti-cancer agent (*e.g.*, cisplatin, adriamycin, and/or taxane) being utilized; the particular tumor cells being treated and the particular host being treated. The method and order of administration of an arsenic compound(s) and other anti-cancer medicament(s) for a given set of conditions can be ascertained by those skilled in the art using conventional techniques and in view of the information set out herein.

[0037] The arsenic compound(s) of the present invention and cisplatin, adriamycin, docetaxel, paclitaxel and/or other cytotoxic anti-cancer agent can be administered as part of a combination therapy or co-therapy. Therefore, "combination therapy" (or "co-therapy") embraces the administration of the arsenic compound(s) and cisplatin or other cytotoxic anti-cancer agent of the invention as part of a specific treatment regimen intended to provide a beneficial effect from the synergistic co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner or simultaneously, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner.

[0038] Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, direct absorption through mucous membrane tissues, and combinations thereof. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected can be administered by intravenous injection, *e.g.*, cisplatin or arsenic trioxide, while the other therapeutic agent, *e.g.*, sodium meta arsenite can be administered orally. Alternatively, for

example, both or all therapeutic agents can be administered by intravenous injection or infusion. The sequence in which the therapeutic agents are administered is not critical.

[0039] "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients (such as, but not limited to, a different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). Where the combination therapy further comprises radiation treatment, the r adiation treatment can be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

[0040] The term "therapeutically effective" is intended to qualify the amount of each agent that will achieve the goal of improvement in tumor size or malignant or neoplastic disease severity and the frequency of neoplastic disease over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. A "therapeutic effect" or "therapeutic effective amount" is also intended to qualify the amount of an anticancer agent required, in combination or composition with one or more other anticancer agent, to relieve to some extent one or more of the symptoms of a neoplasia disorder, including, but is not limited to: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, or stopping) of cancer cell infiltration into peripheral organs; 3) inhibition (i.e., slowing to some extent, or stopping) of tumor metastasis; 4) inhibition, to some extent, of tumor growth; 5) relieving or reducing to some extent one or more of the symptoms

associated with the disorder; and/or 6) relieving or reducing the side effects associated with the administration of anticancer agents.

[0041] The invention provides a pharmaceutical composition, kit and method for combination therapy treatment or prevention and inhibition of the growth of solid tumors, leukemias or metastasis, which involves the administration of sodium meta arsenite and/or arsenic trioxide with cisplatin, adriamycin, docetaxel, paclitaxel and/or other cytotoxic anti-cancer agent in effective amounts to a subject in need of treatment. In certain embodiments, the invention provides a pharmaceutical composition, kit and method including combination therapy for treatment of lung cancer or prevention of the metastasis of lung cancer to other sites or organs in the patient.

[0042] The invention also provides a kit comprising sodium meta arsenite and/or arsenic trioxide and cisplatin, adriamycin, docetaxel, paclitaxel, and/or other cytotoxic anti-cancer agent together in a composition or separate compositions for a combination therapy, in accordance with the invention. The kit can be a package which houses a container or containers that contain the arsenic compound(s) and cisplatin, adriamycin, docetaxel, paclitaxel and/or other cytotoxic anti-cancer agent, and also houses instructions for administering the composition(s) to a subject. In particular, a kit can comprise instructions for simultaneous, separate or sequential use. A kit can contain a single dosage form or it can contain separate dosage forms, *i.e.* one for each therapeutic agent to be administered. In one embodiment, the kit comprises a fixed ratio dosage of the arsenic compound(s) and cisplatin or other cytotoxic anti-cancer agent. The kit can also contain multiple doses of each of the anti-cancer agents, whether combined or separately formulated.

[0043] The kit can additionally include other materials desirable from a commercial and user standpoint, including, without limitation, buffers, diluents, filters, needles, syringes, and package inserts with instructions for performing any methods disclosed herein (e.g., methods for treating a disease disclosed herein). A medicament or formulation in a kit of the invention can comprise any of the combinations, or compositions disclosed herein.

[0044] In aspects of the invention, the kits can be useful for any of the methods disclosed herein including, without limitation, treating a subject having or at risk of developing cancer, solid tumor, or lung cancer.

Formulation

[0045] The active ingredients of the invention are formulated into pharmaceutical preparations (e.g., together in a composition or separately to be used in a combination therapy) for administration to mammals for treatment of cancer.

[0046] For oral administration, the pharmaceutical preparation can be in liquid form, for example, solutions, syrups or suspensions, or can be presented as a drug product for reconstitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinyl pyrrolidone or hydroxypropyl methylcellulose); fillers (e g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e. g.,

magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets can be coated by methods well-known in the art.

[0047] Preparations for oral administration can be suitably formulated to give controlled release of the active compound. For oral administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

[0048] For administration 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 can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0049] The therapeutic agents can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Such formulations are sterile. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0050] The compounds can 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.

[0051] In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as emulsion in acceptable oils) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophilic drugs.

[0052] The pharmaceutical preparations can, if desired, be presented in a pack or dispenser device which can contain one or more unit dosage forms containing the active ingredient. The pack can for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration.

Method of Administration

[0053] It will be recognized by one of skill in the art that the content of the active ingredients in the pharmaceutical preparations of this invention can vary quite widely depending upon numerous factors such as, the desired dosage and the pharmaceutically acceptable carrier being employed. For administration, the dosage amount of the arsenic compound will usually be in the range of from about 0.1 mg/kg to about 100 mg/kg, in certain embodiments from about 1.0 to about 50 mg/kg, in other embodiments from about 2.5 to about 25 mg/kg, and in other embodiments from about 3 to about 15 mg/kg.

[0054] In some embodiments of the invention, the cisplatin-containing pharmaceutical compositions of the invention will contain cisplatin in an amount from about 0.1 mg/ml to about 500 mg/ml, or about 1 mg/ml to about 50 mg/ml, and in other embodiments, from about 1 to 5 mg/ml. Mannitol and/or sodium chloride can be included in amounts conventional for cisplatin preparations. Physiological pH of injectables or infusion drug combinations will be established by inclusion of buffering agents as is known in the art.

[0055] When other cytotoxic anti-cancer agents are used in place of cisplatin, the amount is determined on the basis of the properties of the agent used. For example, adriamycin may be administered at a dose of 60 mg/m^2, administered as a continuous infusion through a central venous catheter or for example, as a 15- or 25-day courses of ADM at a mean dose of about 3.8 mg/m^2 (2.2–4.5 mg/m^2) infused by programmable portable pump. Similarly, docetaxel or paclitaxel (or other taxane) can be given as a high-dose chemotherapeutic agent, for example, 250 mg/m^2 once every three weeks, once every two weeks, or in low doses, less than 100 mg/m^2 on a weekly basis, for example. In some cases, a taxane, *e.g.*, docetaxel or paclitaxel may be given slowly during a 24-hour infusion. The skilled practitioner can determine the appropriate dose of anti-cancer agent and time course of delivery depending on several factors including the relative health of the patient and the type and stage of the cancer, as well as the other drugs administered in the combination therapy.

[0056] The appropriate pharmaceutically acceptable carriers and diluents to be utilized in the pharmaceutical preparations of the invention are well known to those skilled in the art of formulating compounds into pharmaceutical compositions. The pharmaceutical preparations of the invention that are in a form suitable for parenteral administration can be formulated for intravenous infusion or injection in numerous ways well known to those skilled in the art with pharmaceutically acceptable carriers. In certain embodiments, such pharmaceutical preparations

are in the form of a freeze-dried mixture of the active ingredients in a unit dosage form, prepared by conventional techniques, which can be reconstituted with water or other suitable infusion liquid at the time of administration.

[0057] For the treatment of breast cancer and many other forms of solid tumors, as well as in treatment of leukemias and lung cancer, the arsenic compounds of the invention are more likely to be administered systemically, in a pharmaceutical composition containing such excipients or inert components, which are well known in the art pertaining to chemotherapy of tumors. More specifically, if an arsenic compound of the invention is to be administered systemically, it can be confected as a powder, pill, tablet or the like or as a syrup or elixir suitable for oral administration. For intravenous or intraperitoneal administration, the arsenic compound will be prepared as a solution or suspension capable of being administered by injection. In certain cases, it can be useful to formulate these compounds by injection. In certain other cases, it can be useful to formulate these compounds in suppository form or as extended release formulation for deposit under the skin or intramuscular injection.

[0058] The arsenic compound of the invention will be administered as a chemotherapeutic agent together with cisplatin in a useful therapeutic dose which will vary from condition to condition and which, in certain instances can vary with the severity of the condition being treated and the patients susceptibility to treatment. Accordingly, no single dose will be uniformly useful, but will require modification depending on the particularities of the tumor or malignancy being treated. Such doses can be arrived at through routine experimentation. For the treatment of solid tumors and leukemias, particularly breast cancer and acute myeloid leukemia, it is anticipated that the arsenic compounds of the invention will be administered for approximately 1 to 8 weeks to a patient in need thereof, in a dose that is effective to halt, slow

the growth or dissipate the tumor or halt leukemia cell proliferation. In certain embodiments of the invention, the arsenic compound is sodium meta arsenite, which is to be administered orally, in a daily dose which in some embodiments of the invention will be in the range of an approximately 0.0001 mg/kg per day to 100 mg/kg per day; or in the range of 0.05 mg/kg to 50 mg/kg per day; or in other embodiments, in the range of 1 mg to 25 mg per day; and in other embodiments in the range of 2 mg/kg to 20 mg/kg per day or 2.5 to 10 mg/kg per day. However, the dose can be adjusted upward or downward to suit the needs of any particular patient.

[0059] The cisplatin or other cytotoxic anti-cancer agent component of the combination therapy can be administered in accordance with the invention in the same manner as known in clinical practice. For example, slow intravenous infusion is the method of choice for cisplatin. For promoting diuresis when using cisplatin, the incorporation of mannitol in a dextrose/saline solution is the preferred carrier. The protocol can also include prehydration of the patient by administration of a dextrose/saline solution before administration of the cisplatin, adriamycin, docetaxel and/or paclitaxel. In some embodiments of the invention, the dosage of cisplatin, when administered with an arsenic compound in accordance with the invention, is a single dose of from about 3 to about 100 mg/m^2 of cisplatin, and in certain embodiments is delivered at the end of a one to five consecutive day course of treatment with the arsenic compound. In other embodiments, the dose of cisplatin is about 20 mg/m^2 or more once every three to four weeks. Alternatively, therapeutically appropriate amounts of other cytoxic agents, e.g., adriamycin, docetaxel and/or paclitaxel can be administered to the patient. Infusions of cisplatin, adriamycin, docetaxel and/or paclitaxel or other cytotoxic agent can be given one to two times weekly, and the weekly treatments repeated several times unless renal toxicity, neurotoxicity or other side effects provide a contraindication.

[0060] For parenteral administration of arsenic trioxide, the course of therapy generally employed is from 0.0001 to 100 mg/kg per day for about five consecutive days, or 0.001 to 50 mg/ml, and in other embodiments, 0.01 to 20 mg/kg for about five consecutive days. In some embodiments of the invention, the dosage range of arsenic trioxide to be used in combination with cisplatin is about 0.1 to 5.0 mg/kg per day. The skilled practitioner can determine the appropriate amount and course for the administration of arsenic trioxide and adjust the treatment protocol accordingly.

EXAMPLE 1:

[0061] ***In vitro Studies with cisplatin and sodium meta arsenite.*** Both cisplatin and sodium meta arsenite can cause telomere damage. Therefore, the combination of these two anti-cancer agents was tested to determine whether the two drugs show evidence of *in vitro* synergy in two non-small cell lung cancer cell lines. H460 (4kb, IC50, IC50=10μM) and A549 (6kb, IC50=13μM) were chosen, because they have relatively short telomeres and are part of a National Cancer Institute (NCI) 60 cell line panel. IC50 concentrations for cisplatin and KML001 were determined by MTT assay and the widely accepted median effect methodology by Chou and Talalay (Advances in Enzyme Regulation (1984), 22:27-55), based on fixed IC50 ratios used for determination of synergy, additivity or antagonism (Fig. 1A-1C).

[0062] ***Cell culture and MTT assay.*** Cells were grown under standard conditions (5% CO_2,/37°C/humidified atmosphere) in their respective recommended media such as RMPI 1640, Iscove's or DMEM (Invitrogen) and passaged routinely. For MTT proliferation assays, exponentially growing cells were harvested and plated in 96-well plates (2,000/well). To assess the growth inhibitory potential of drugs, test drugs were added at concentrations ranging

nM to 100 μM. To determine cell growth at the time of drug addition (d0), which enables calculation of the actual cell kill, one of the 96-well plates was immediately developed after drug addition. The others were incubated for 5 days before 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) was added and the conversion to purple formazan by viable cells was measured using a SynergyHT plate reader (550 nm) and K4C software (BioTEK). Formazan was dissolved with DMSO. Growth curves were generated in MSExcel and growth inhibitory concentration 50 and 100% as well as net cell kill were determined. The results are presented in Figures 1A-C and Tables 2-4.

[0063] A549 and H460 have an IC50 for cisplatin of 1.5 and 1 μM respectively, but are relatively insensitive to sodium meta arsenite although H460 cells, which have shorter telomeres (4 kb) have a lower IC50 than A549 cells with relatively longer telomeres (6 kb, Fig. 1A). When the two drugs were combined, however, a very marked synergism was obtained for most levels of effect (Fig. 1B-C, Tables 2-4). Combination indices (CI) of well below 1 were found for the effective dose (ED) levels 50, 75 and 90 % (Table 2), reducing, *e.g.,* the IC50 of cisplatin from 1.5 μM to 0.45 μM in A549 cells (Fig. 1A). Thus, KML001 is able to sensitize lung cancer cell lines to cisplatin.

Table 2 Combination Index Values

Cell Line	CI ED 50	CI ED75	CI ED90
A549	0.86	0.75	0.68
H460	0.33	0.16	0.09

Table 3 Single Agent Index Values: H460 Cells

μM	Sodium Meta Arsenite	Cisplatin	Sodium Meta Arsenite-Cisplatin
IC50	10	1	0.7
IC75	20	1.7	1
IC90	30	2.5	1.5

Table 4 Single Agent Index Values: A549 Cells

μM	Sodium Meta Arsenite	Cisplatin	Sodium Meta Arsenite-Cisplatin
IC50	13	1.5	0.457
IC75	19	2	0.7
IC90	17	4	1.1

[0064] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein.

WHAT IS CLAIMED IS:

1. An anti-cancer agent comprising

- a first composition comprising sodium meta arsenite and a pharmaceutically acceptable carrier and

- a second composition comprising cisplatin, docetaxel or paclitaxel and a pharmaceutically acceptable carrier.

2. The anti-cancer agent according to claim 1 wherein the first composition comprises sodium meta arsenite and the second composition comprises cisplatin.

3. The anti-cancer agent according to claim 1 wherein the first composition comprises sodium meta arsenite and the second composition comprises docetaxel or paclitaxel.

4. The anti-cancer agent according to any one of claims 1 to 3, wherein the first composition is formulated for oral administration.

5. The anti-cancer agent according to any one of claims 1 to 4, wherein the second composition is formulated for intravenous infusion or injection.

6. The anti-cancer agent according to any one of claims 1 to 5, wherein the anti-cancer agent is for treatment of lung cancer.

7. The anti-cancer agent according to any one of claims 1 to 6, wherein the anti-cancer agent is for treatment of cancer cells containing chromosomes having telomeres of from 4 to 6Kb.

8. The anti-cancer agent according to any one of claims 1 to 6, wherein the anti-cancer agent is for treatment of prostate cancer.

9. Use of the anti-cancer agent defined in any one of claims 1 to 5 for treatment of lung cancer.

10. Use of the anti-cancer agent defined in any one of claims 1 to 5 for treatment of cancer cells containing chromosomes having telomeres of from 4 to 6Kb.

11. Use of the anti-cancer agent defined in any one of claims 1 to 5 for treatment of prostate cancer.

12. Use of the anti-cancer agent defined in any one of claims 1 to 5 for the preparation of a medicament for the treatment of lung cancer.

13. Use of the anti-cancer agent defined in any one of claims 1 to 5 for the preparation of a medicament for the treatment of cancer cells containing chromosomes having telomeres of from 4 to 6Kb.

14. Use of the anti-cancer agent defined in any one of claims 1 to 5 for the preparation of a medicament for the treatment of prostate cancer.

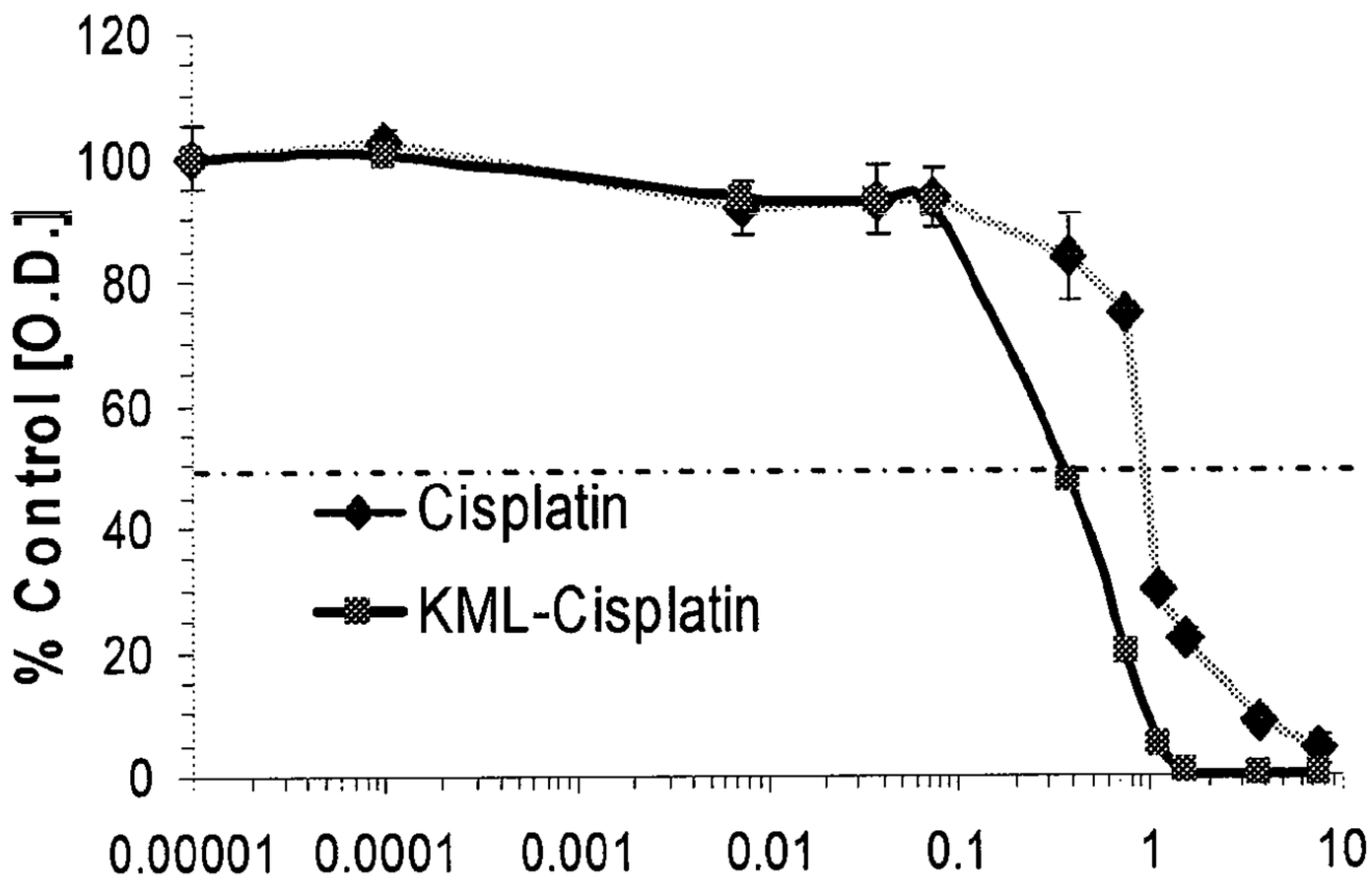

120
100
80
60
40
20
0
% Control [O.D.]
Cisplatin
KML-Cisplatin
0.00001
0.0001
0.001
0.01
0.1
1
10
Sodium Meta Arsenite [μM]

FIG. 1A

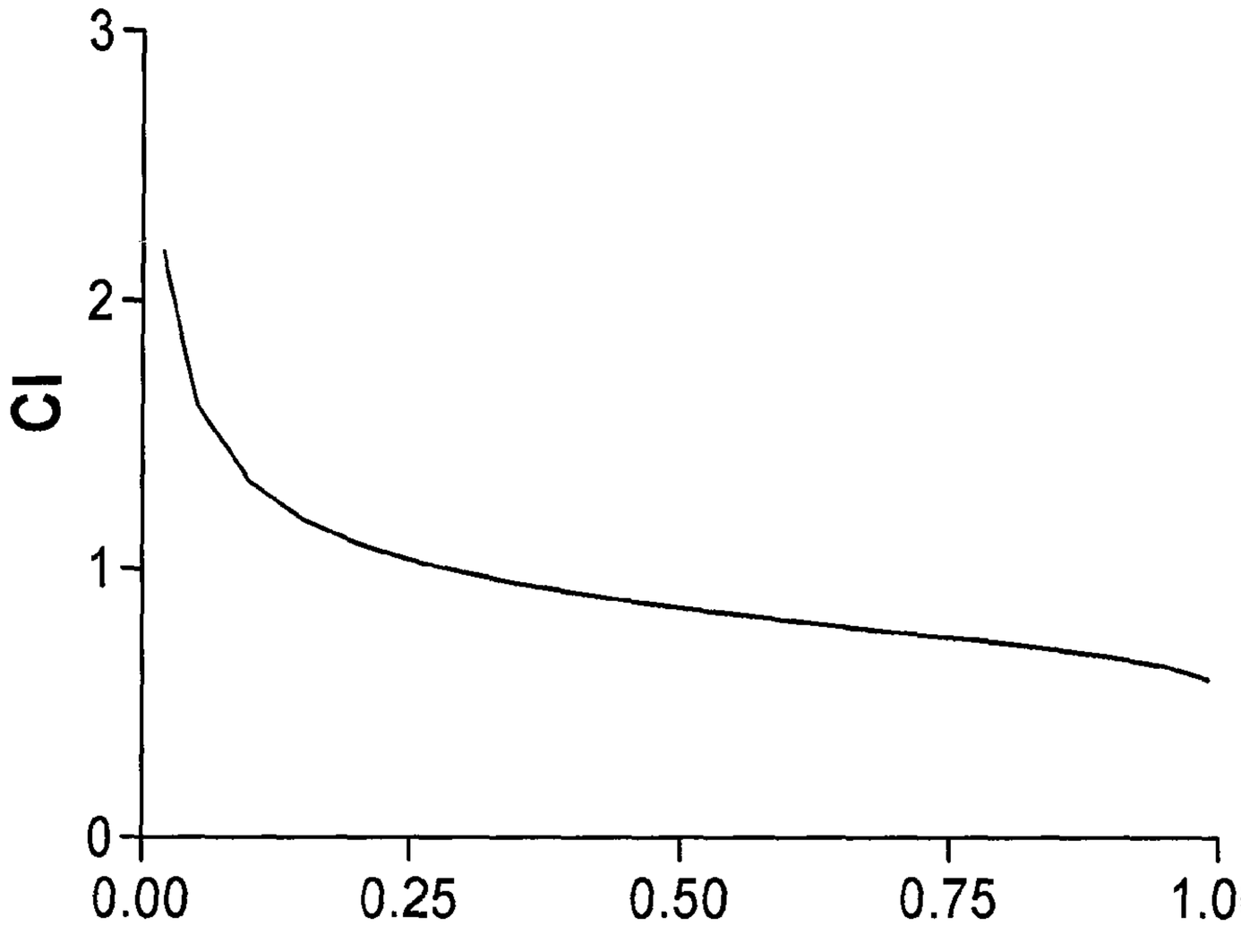


FIG. 1B

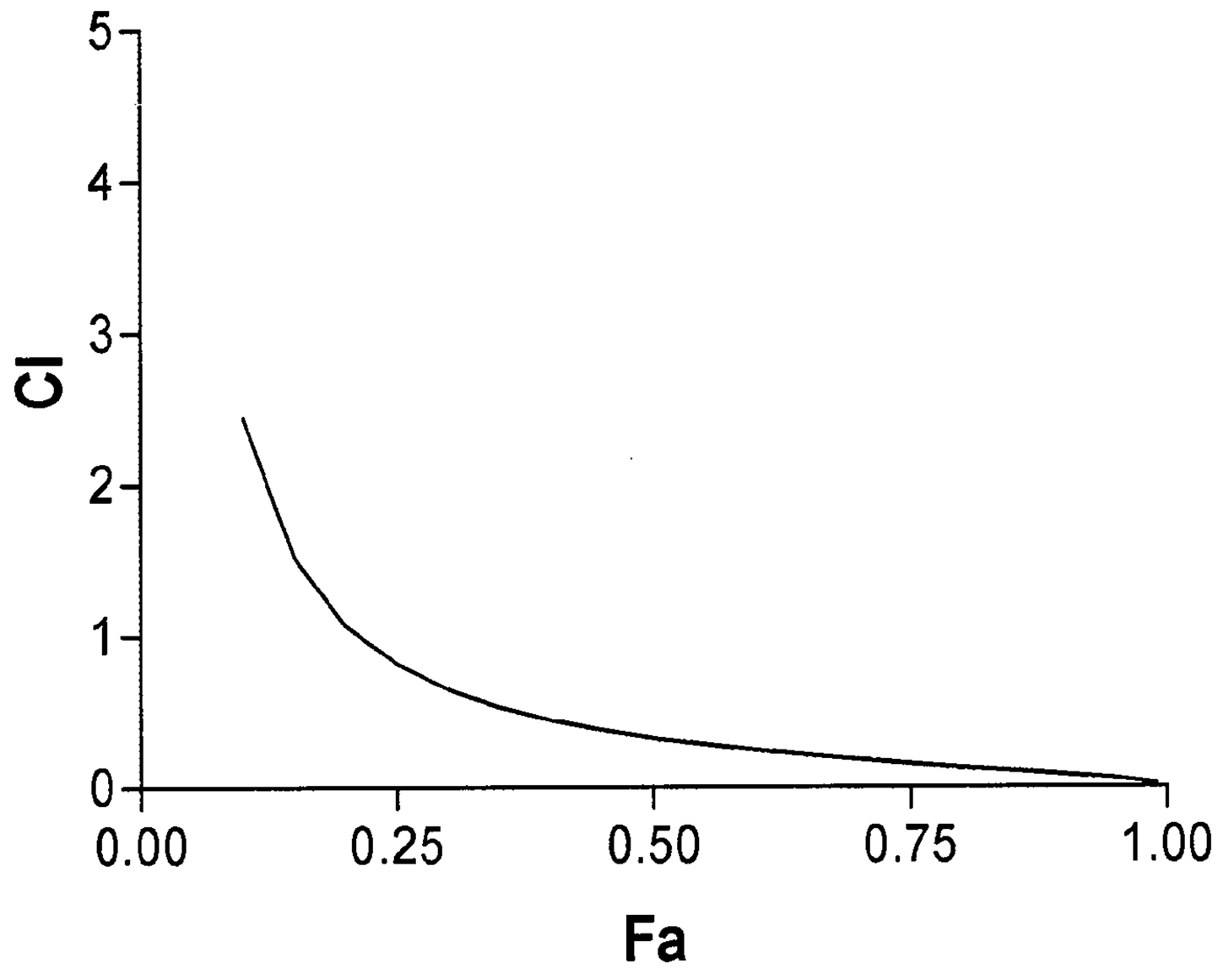
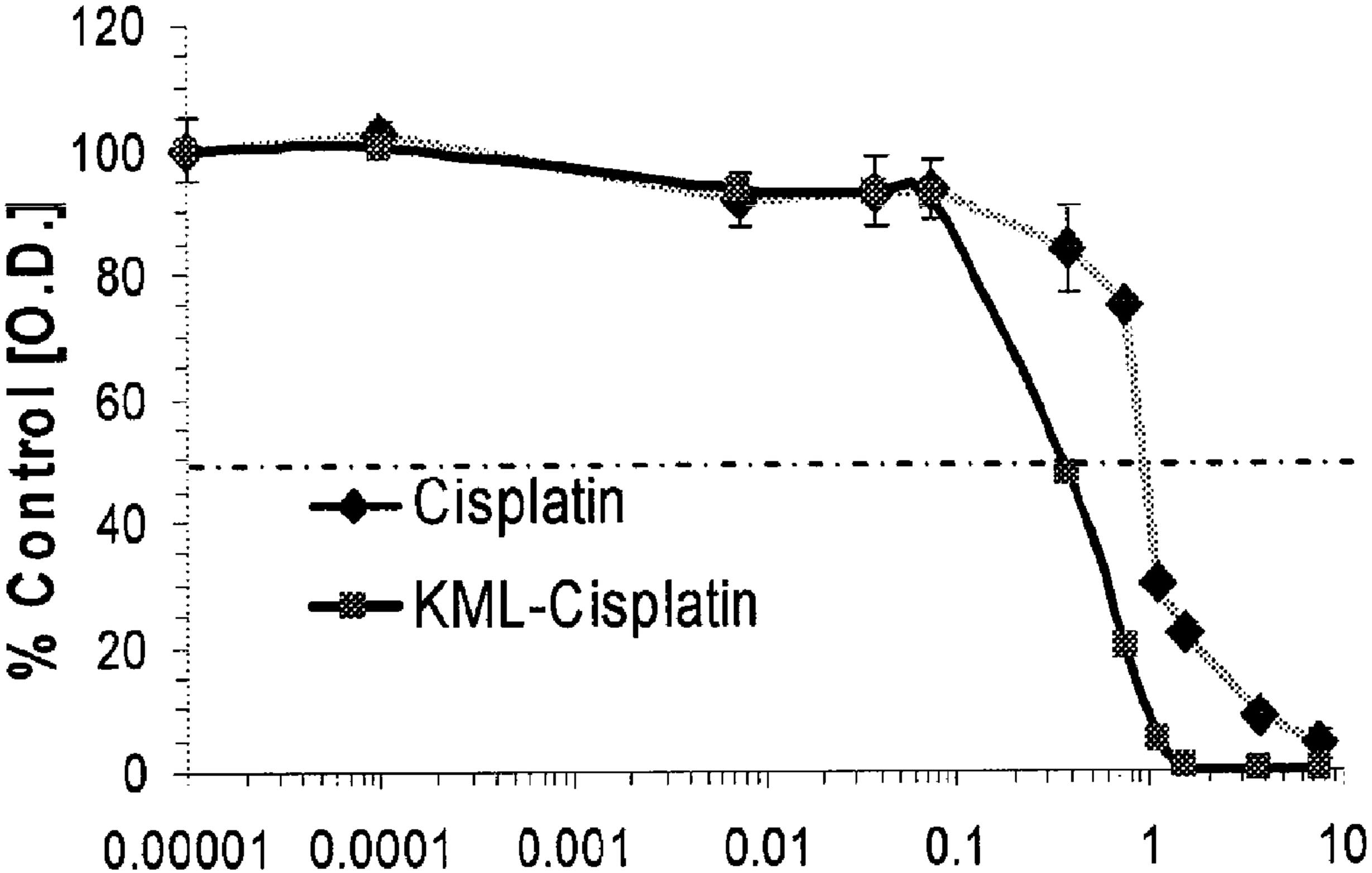


FIG. 1C


120
100
80
60
40
20
0
% Control [O.D.]
Cisplatin
KML-Cisplatin
0.00001
0.0001
0.001
0.01
0.1
1
10
Sodium Meta Arsenite [μM]