



(86) Date de dépôt PCT/PCT Filing Date: 2007/07/04
(87) Date publication PCT/PCT Publication Date: 2008/01/10
(45) Date de délivrance/Issue Date: 2012/08/28
(85) Entrée phase nationale/National Entry: 2009/01/06
(86) N° demande PCT/PCT Application No.: IL 2007/000836
(87) N° publication PCT/PCT Publication No.: 2008/004231
(30) Priorités/Priorities: 2006/07/07 (US60/819,164);
2007/01/12 (US60/880,107)

(51) Cl.Int./Int.Cl. *A61K 31/675* (2006.01),
A61K 31/196 (2006.01), *A61K 31/203* (2006.01),
A61K 31/415 (2006.01), *A61K 31/425* (2006.01),
A61K 31/4402 (2006.01), *A61K 45/06* (2006.01),
A61P 35/00 (2006.01)

(72) Inventeur/Inventor:
BEN-SASSON, SHMUEL A., IL

(73) Propriétaire/Owner:
TILTAN PHARMA LTD., IL

(74) Agent: NORTON ROSE CANADA
S.E.N.C.R.L., S.R.L./LLP

(54) Titre : TRAITEMENT ANTICANCEREUX FAISANT APPEL A UN H2-BLOQUANT, A AU MOINS UN AGENT ANTI-INFLAMMATOIRE ET A UN AGENT CYTOTOXIQUE
(54) Title: ANTI-CANCER THERAPY COMPRISING AN H2-BLOCKER, AT LEAST ONE ANTIINFLAMMATORY AGENT AND A CYTOTOXIC AGENT

(57) **Abrégé/Abstract:**

The present invention relates to the treatment of a mammal with a pharmaceutical composition comprising an H2-blocker, at least one anti-inflammatory agent, a cytotoxic agent and, optionally, levamisole, a retinoid, an NFkB inhibitor, a redox quinone, an agent that enhances the intracellular accumulation of NADH + H⁺, a poly-alcohol, an inhibitor of pro-angiogenic growth factor(s) and an MMP inhibitor, such pharmaceutical composition allowing for the enhanced therapy and/or prevention of neoplastic diseases and disorders.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 January 2008 (10.01.2008)

PCT

(10) International Publication Number
WO 2008/004231 A1

(51) International Patent Classification:

A61K 31/675 (2006.01) A61K 31/425 (2006.01)
A61K 45/06 (2006.01) A61K 31/4402 (2006.01)
A61K 31/196 (2006.01) A61P 35/00 (2006.01)
A61K 31/415 (2006.01) A61K 31/203 (2006.01)

(21) International Application Number:

PCT/IL2007/000836

(22) International Filing Date: 4 July 2007 (04.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/819,164 7 July 2006 (07.07.2006) US
60/880,107 12 January 2007 (12.01.2007) US

(71) Applicant (for all designated States except US): **TILTAN PHARMA LTD.** [IL/IL]; 5 Hamarpeh Street, 91450 Jerusalem (IL).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BEN-SASSON, Shmuel A.** [IL/IL]; 9 Beit-Hakerem Street, 96343 Jerusalem (IL).

(74) Agent: **REINHOLD COHN AND PARTNERS**; P.O.Box 4060, 61040 Tel Aviv (IL).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTI-CANCER THERAPY COMPRISING AN H2-BLOCKER, AT LEAST ONE ANTIINFLAMMATORY AGENT AND A CYTOTOXIC AGENT

(57) Abstract: The present invention relates to the treatment of a mammal with a pharmaceutical composition comprising an H2-blocker, at least one anti-inflammatory agent, a cytotoxic agent and, optionally, levamisole, a retinoid, an NFkB inhibitor, a redox quinone, an agent that enhances the intracellular accumulation of NADH + H⁺, a poly-alcohol, an inhibitor of pro-angiogenic growth factor(s) and an MMP inhibitor, such pharmaceutical composition allowing for the enhanced therapy and/or prevention of neoplastic diseases and disorders.



WO 2008/004231 A1

ANTI-CANCER THERAPY COMPRISING AN H₂-BLOCKER, AT LEAST ONE ANTIINFLAMMATORY AGENT AND A CYTOTOXIC AGENT

TECHNICAL FIELD OF THE INVENTION

5 The present invention relates to the field of anti-cancer therapy and/or prevention.

BACKGROUND OF THE INVENTION

10 Cancer generally refers to one of a group of more than 100 diseases caused by the uncontrolled, abnormal growth of cells that can spread to adjoining tissues or other parts of the body. Cancer cells can form a solid tumor, in which the cancer cells are massed together, or exist, as dispersed cells, as in leukemia. Normal cells divide until maturation is attained and then only as necessary for replacement of damaged or dead cells. Cancer cells are often referred to as "*malignant*", because they divide endlessly, eventually crowding out nearby tissues and spreading to other parts of the body. The
15 tendency of cancer cells to invade and spread from one organ to another or from one part of the body to another distinguishes them from benign tumor cells, which overgrow but do not spread to other organs or parts of the body. Malignant cancer cells eventually metastasize and spread to other parts of the body via the bloodstream or lymphatic system, where they can multiply and form new tumors. This sort of tumor progression
20 makes cancer a deadly disease.

Although there have been great improvements in the diagnosis and treatment of cancer, many people die from cancer each year, and their deaths are typically due to metastases and cancers that are resistant to conventional therapies.

25 Most drug-mediated cancer therapies rely on poisons, called cytotoxic agents, selective for dividing cells. These drugs are effective because cancer cells generally divide more frequently than normal cells. However, such drugs almost inevitably do not kill all of the cancer cells in the patient. One reason is that cancer cells can acquire mutations that confer drug resistance. Another is that not all cancer cells divide more frequently than normal cells, and slowly- dividing cancer cells can be as, or even more,

- 2 -

insensitive to such cytotoxic agents as normal cells. Some cancer cells divide slowly, because they reside in a poorly vascularized, solid tumor and are unable to meet the needs required for cell division. For example, cytotoxic agents such as cyclophosphamide have been used to treat cancer.

5 Although cancer chemotherapy has advanced dramatically in recent years, treating cancers with a single agent has had limited success. Firstly, any single agent may only target a subset of the total population of malignant cells present, leaving a subpopulation of cancerous cells to continue growing. Secondly, cells develop resistance upon prolonged exposure to a drug. Combination therapies, which employ two or more
10 agents with differing mechanisms of action and differing toxicities, have been useful for circumventing drug resistance and increasing the target cell population, but have not proven effective in the treatment of all cancers. In addition, certain combinations of agents may be synergistic: their combined effect is larger than that predicted based on their individual activities. Thus, combining different agents can be a powerful strategy for
15 treating cancer.

 The most striking difference between malignant and healthy cells is the capacity of cancer cells for unrestricted proliferation. This difference is exploited by many cytotoxic agents, which typically disrupt cell proliferation by interfering with the synthesis or integrity of DNA. Examples of classes of cytotoxic agents which function in
20 this manner include alkylating agents, such as cyclophosphamide, antimetabolites (e.g. purine and pyrimidine analogues), and platinum coordination complexes.

 One problem with cytotoxic agents which function by disrupting cell division is that they do not discriminate between normal and malignant cells: any dividing cell is a potential target for their action. Thus, cell populations which normally exhibit high levels
25 of proliferation (such as bone marrow) are affected, leading to the toxic side effects commonly associated with cancer treatments.

 As a tumor grows, it requires blood supply and, consequently, growth of new vasculature. Angiogenesis is a process of tissue vascularization that involves the growth of new developing blood vessels into a tissue, and is also referred to as neo-
30 vascularization. Blood vessels are the means by which oxygen and nutrients are supplied to living cells.

- 3 -

Inhibitors of pro-angiogenic growth factors are agents used to inhibit the signaling of known pro-angiogenic factors like VEGF or FGF. Currently, these agents by themselves failed to demonstrate sufficient efficacy in the treatment of cancer.

With only a few exceptions, no single drug or drug combination is curative for most cancers. Thus, new drugs or combinations that can delay the growth of life-threatening tumors and/or improve quality of life by further reducing tumor load are needed.

Natori et al. (*Biomedicine & Pharmacotherapy*, 59: 56-60 (2005)) showed that Cimetidine, an H₂-blocker, has anti-angiogenic properties and therefore anti-cancer properties. On the other hand, US Patent Application 20030158118 (by Weidner, Morten and Sloth) showed that Cimetidine by itself did not inhibit tumor growth to any significant amount (Example 4 therein). Additionally, Saarloos MN et al. (*Clin. Exp. Metastasis* 11: 275-83 (1993)) performed immunotherapy tests on metastasis by administration of indomethacin plus interleukin-2 (IL-2), and showed that the addition of an H₂-blocker did not improve the therapeutic efficacy. On the other hand, US Patent Application 20030158118 suggested a cancer treatment composed of Cimetidine and a cysteine derivative.

Levamisole is a synthetic phenylimidothiazole which has been known in the art as an antihelminthic agent. While several studies failed to demonstrate any beneficial effect of Levamisole, by itself or in combination with 5-FU, others found some benefit for Levamisole when combined with 5-FU (DeVita et al. *Cancer: Principles and Practice of Oncology*, 5th Edition, pp 1171-5).

Quinones are known for their ability to induce oxidative stress through redox cycling, hereby referred to as "Redox quinones" (Powis G., *Free Radic. Biol. Med.* 6:63-101 (1989)). Pharmaceutically acceptable redox quinones such as Vitamin K₃ have special therapeutic value since they are required for the bioactivation of proteins involved in hemostasis. Vitamin K₃ is a redox quinone, known as a prothrombogenic agent, mainly in supplement of veterinary diet. Studies have shown that Vitamin K₃ has failed to demonstrate beneficial anti-cancer properties (Tetef M. et al. *J. Cancer Res. Clin. Oncol.* 121:103-6 (1995)).

- 4 -

Retinoids are a class of chemical compounds that are related chemically to vitamin A. Retinoids are used in medicine, primarily due to the way they regulate epithelial cell growth. A natural retinoid, all-trans retinoic acid (ATRA), regulates a variety of important cellular functions via the retinoic acid receptor (RAR). ATRA has therapeutically been used against various malignancies including acute promyelocytic leukemia. Anti-tumor effects of retinoids are attributed to their influence on cell proliferation, differentiation, apoptosis and angiogenesis. However, there is still some uncertainty with respect to ATRA role in angiogenesis. For example, Saito A. et al. (*Endocrinology* 148:1412-23 (2007)) claimed that ATRA has a pro-angiogenic effect.

US patent application No. US2005/148521 relates to methods and compositions for treating cancer comprising administering a combination of an effective amount of cytotoxic agent, a non steroidal anti inflammatory drug (NSAID), an ester of benzoic acid and a pharmaceutically acceptable carrier

WO 06/056889 relates to methods and pharmaceutical compositions for inhibiting angiogenesis, comprising administering a combination of at least one angiogenesis inhibitor, at least one agent that enhances accumulation of intracellular NADH+ H+ and a pharmaceutically acceptable carrier.

SUMMARY OF THE INVENTION

It has now surprisingly been found by the inventors of the present invention that a pharmaceutical composition comprising an H2-blocker (e.g. Cimetidine) with a cytotoxic agent and at least one anti-inflammatory drug (e.g. NSAID), augments the anti-tumor effect significantly when compared to the activity of each agent by itself.

Additionally, it has unexpectedly been found that further addition of an NFkB inhibitor (such as sulfasalazine) to a pharmaceutical composition comprising an H2-blocker, a cytotoxic agent, and at least one anti-inflammatory drug (e.g. NSAID) further enhances this anti-tumor effect.

Additionally, it has unexpectedly been found that further addition of a retinoid (such as all-trans retinoic acid (ATRA)) to a pharmaceutical composition comprising an H2-blocker, a cytotoxic agent, and at least one anti-inflammatory drug (e.g. NSAID)

- 5 -

further enhances this anti-tumor effect.

Additionally, it has unexpectedly been found that addition of Levamisole to a pharmaceutical composition comprising an H₂-blocker, a cytotoxic agent, and at least one anti-inflammatory drug (e.g. NSAID) promotes and enhances the anti-tumor activity of said drug combination.

Additionally, it has unexpectedly been found that addition of Levamisole to a pharmaceutical composition comprising an H₂-blocker, a cytotoxic agent, at least one anti-inflammatory drug (e.g. NSAID) and an NFκB inhibitor promotes and enhances the anti-tumor activity of said drug combination.

Other agents, such as agents that enhance the intracellular accumulation of NADH + H⁺, inhibitors of a matrix metalloproteinase and inhibitors of pro-angiogenic factor(s) were also incorporated in the pharmaceutical compositions of the subject invention and unexpectedly showed an enhancement of anti-tumor effects.

The present invention thus provides a pharmaceutical composition comprising an H₂-blocker, at least one anti-inflammatory agent, a cytotoxic agent and optionally, Levamisole, an NFκB inhibitor, a retinoid, a redox quinone, an agent that enhances the intracellular accumulation of NADH + H⁺, a poly-alcohol, an inhibitor of pro-angiogenic growth factor(s) and an MMP inhibitor and the use thereof for the treatment and/or prevention of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Tumor size (in mm³) after 40 days from tumor cell inoculation and administration of several pharmaceutical compositions of the present invention.

Figure 2: Tumor size (in mm³) after 28 days from tumor cell inoculation and administration of cimetidine and/or levamisole.

Figure 3: Tumor size (in mm³) after 28 days from tumor cell inoculation and administration of several pharmaceutical compositions of the present invention.

Figure 4: Tumor size (in mm³) after 28 days from tumor cell inoculation and administration of several pharmaceutical compositions of the present invention.

Figure 5: Tumor size (in mm³) after 28 days from tumor cell inoculation and administration of several pharmaceutical compositions of the present invention.

- 6 -

Figure 6: Tumor size (in mm³) after 28 days from tumor cell inoculation and administration of several pharmaceutical compositions of the present invention.

Figure 7: Tumor size (in mm³) after 35 days from tumor cell inoculation and administration of several pharmaceutical compositions of the present invention.

5

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical composition comprising: an H2-blocker, at least one anti-inflammatory agent, a cytotoxic agent and a pharmaceutically acceptable carrier.

10 The term "*H2-blocker*" as referred to in the present invention relates to an Histamine type 2-receptor antagonist, used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. The H2-blocker may be any H2-blocker known to those skilled in the art. For example, the H2-blocker may be selected from the group consisting of Cimetidine, Ranitidine, Famotidine and Nizatidine.

15 The term "*anti-inflammatory agent (drug)*" as used herein relates to any agents capable of reducing and/or inhibiting and/or preventing inflammation disease caused by either response to infection, injury, irritation, or surgery. In one embodiment of the invention, the anti-inflammatory agent may be selected from the group consisting of steroidal and non-steroidal anti-inflammatory agents. In another embodiment the anti-
20 inflammatory drug is a steroidal anti-inflammatory drug selected from a group consisting of dexamethasone and betamethasone. In a further embodiment the anti-inflammatory agent is a non-steroidal anti inflammatory drug. In a specific embodiment the non-steroidal anti-inflammatory drug may be selected from a COX-1 inhibitor, a COX-2 inhibitor and a non-selective COX-1 and COX-2 inhibitor. In yet a further embodiment of
25 the invention, the COX-1 and COX-2 inhibitors may be selected from the group consisting of diclofenac, piroxicam and indomethacin. In another embodiment, in addition to the non-steroidal anti-inflammatory drug, the composition further comprises a steroidal anti-inflammatory drug such as, but not limited to, dexamethasone and betamethasone.

- 7 -

The term "*cytotoxic agent*" as used herein relates to any agent used for the treatment of abnormal and uncontrolled progressive cellular growth. A cytotoxic agent acts as an angiogenesis inhibitor when administered at a low dose. Non limiting examples of cytotoxic agents include the alkylating agents cyclophosphamide (CTX) (Bristol-Meyers Squibb), ifosfamide (Bristol-Meyers Squibb), chlorambucil (Glaxo Wellcome), and carmustine (Bristol-Meyers Squibb); the anti-metabolites cytarabine (Pharmacia & Upjohn), 6-mercaptopurine (Glaxo Wellcome), 6-thioguanine (Glaxo Wellcome), and methotrexate (Immunex); the antibiotics doxorubicin (Pharmacia & Upjohn), daunorubicin (NeXstar), and mitoxantrone (Immunex); and miscellaneous agents such as vincristine (Lilly), vinblastine (Lilly), and paclitaxel (Bristol-Meyers Squibb). In one embodiment of the present invention, the cytotoxic agent may be selected from the group consisting of: cyclophosphamide, ifosfamide, cytarabine, 6-mercaptopurine, 6-thioguanine, vincristine, doxorubicin, daunorubicin, chlorambucil, carmustine, vinblastine, methotrexate, mitoxantrone, and paclitaxel or their pharmaceutically acceptable salts. In a further embodiment of the present invention, the cytotoxic agent may be cyclophosphamide or ifosfamide.

In the context of the present invention the term "*pharmaceutically acceptable carrier*" relates to pharmaceutically-acceptable, nontoxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. Such carriers may include, however not limited to, buffering agents, solubilizing agents, stabilizing agents or taste additives.

Each of the components of the pharmaceutical composition of the present invention, i.e. H2-blocker (e.g. cimetidine), cytotoxic agent (e.g. cyclophosphamide) and anti-inflammatory drug (e.g. NSAID), by itself did not demonstrate any significant anti-tumor effects. Example 2 (Group 3, Fig. 2) demonstrates that a single administration of cimetidine did not result in any significant effect on tumor growth. Additionally, Experiments 3 and 4 (Fig. 3 and 4 respectively) in WO03/061566 demonstrated a very moderate effect of cyclophosphamide alone on tumor growth. Thus, it was surprisingly found that a pharmaceutical composition comprising an H2-blocker, a cytotoxic agent and an anti-inflammatory agent gave significant and enhanced anti-tumor effect.

- 8 -

In an embodiment of the present invention a pharmaceutical composition of the invention may further comprise Levamisole.

In a further embodiment of the present invention, a pharmaceutical composition of the invention also comprises an NFkB inhibitor.

5 The term "*NFkB inhibitor*" as used herein relates to any agent used for the inhibition of the *Nuclear Factor kappa B* (NFkB) intracellular transcription factor. In a specific embodiment, the NFkB inhibitor is selected from sulfasalazine, rapamycin, caffeic acid phenethyl ester, SN50 (a cell-permeable inhibitory peptide), parthenolide, triptolide, wedelolactone, lactacystin and MG-132 [Z-Leu-Leu-Leu-H]. In yet a further
10 embodiment, the NFkB inhibitor is selected from sulfasalazine and rapamycin or their derivatives. In another embodiment rapamycin derivatives are selected from temsirolimus and everolimus.

In one embodiment of the invention, the pharmaceutical composition further comprises both Levamisole and an NFkB inhibitor together.

15 In a further embodiment of the present invention, a pharmaceutical composition of the invention also comprises a retinoid.

 The term "*retinoid*" as used herein relates to a class of chemical compounds that are related chemically to vitamin A. As used herein, a retinoid component of the invention is any compound which acts through and/or binds to retinoic acid receptors
20 (RARs) or to retinoid X receptors (RXRs). In a specific embodiment, the retinoid is an all trans retinoic acid (ATRA), known also as tretinoin or vesanoid (Roche Pharmaceuticals). ATRA can be isolated from natural sources or prepared synthetically.

 In yet another embodiment of the present invention, a pharmaceutical composition of the invention may further comprise at least one agent that enhances
25 intracellular accumulation of $\text{NADH} + \text{H}^+$. In a specific embodiment, the agent that enhances intracellular accumulation of $\text{NADH} + \text{H}^+$ is a poly-alcohol. In a further embodiment, the poly-alcohol is selected from the group consisting of xylitol, mannitol, sorbitol, arabinol, iditol and any other polyol known to those of skill in the art. In a specific embodiment, the poly-alcohol is xylitol.

- 9 -

In another embodiment of the present invention, a pharmaceutical composition of the invention may further comprise an inhibitor of a matrix metalloproteinase (MMP).

As used herein, the phrase "*matrix metalloproteinase (MMP) inhibitor*" relates to any chemical compound that inhibits by at least 5%, the hydrolytic activity of at least one
5 matrix metalloproteinase enzyme that is naturally occurring in a mammal.

The MMP inhibitor may be any MMP inhibitor known in the art, such as AG-3340, RO 32-3555, RS 13-0830, Tissue Inhibitors of metalloproteinases (TIMPs) (e.g. TIMP-1, TIMP-2, TIMP-3, or TIMP-4), alpha 2- macroglobulin, tetracyclines (e.g., tetracycline, minocycline, and doxycycline), hydroxamates (e.g. batimastat, marimistat
10 and trocade), chelators (e.g., EDTA, cysteine, acetylcysteine, D-penicillamine, and gold salts), synthetic MMP fragments, succinyl mercaptopurines, phosphonamidates, and hydroxaminic acids. In a specific embodiment, the MMP inhibitor is an MMP2 or an MMP9 inhibitor.

In another embodiment of the present invention, a pharmaceutical composition of
15 the invention may further comprise an inhibitor of a pro-angiogenic growth factor.

The term "*inhibitor of pro-angiogenic growth factor*" relates to agents which are used to inhibit the signaling of known pro-angiogenic factors such as VEGF, FGF or PDGF. Without wishing to be bound by theory, it was shown that these agents can act extracellularly, by the inhibition of the interaction of an angiogenic factor with its
20 receptor or can act intracellularly via the inhibition of the protein-kinase activity of the corresponding receptors. Non limiting examples of these agents include anti-VEGF or anti-VEGF-Receptor antibodies or inhibitors of the protein-kinase domain of VEGF-R, FGF-R or PDGF-R.

In another embodiment of the present invention, a pharmaceutical composition of
25 the invention may further comprise a redox quinone.

Quinones are compounds having a fully conjugated cyclic dione structure, such as that of benzoquinones, derived from aromatic compounds by conversion of an even number of -CH= groups into -C(=O)- groups with any necessary rearrangement of double bonds (polycyclic and heterocyclic analogues are included). Quinones are known for their
30 ability to induce oxidative stress through redox cycling, hereby referred to as "*Redox*

- 10 -

quinones" (Powis G., *Free Radic. Biol. Med.* 6:63-101 (1989)). Pharmaceutically acceptable redox quinones such as Vitamin K₃ have special therapeutic value since they are required for the bioactivation of proteins involved in hemostasis. Vitamin K₃ is a redox quinone, known as a prothrombogenic agent, mainly in supplement of veterinary diet. Studies have shown that Vitamin K₃ has failed to demonstrate beneficial anti-cancer properties (Tetef M. et al. *J. Cancer Res. Clin. Oncol.* 121:103-6 (1995)).

In one embodiment, the redox quinone is Vitamin K₃ (known as menadione or 2-methyl-1,4-naphthalenedione). In a further embodiment, Vitamin K₃ may be selected from a group consisting of menadione and menadione sodiumbisulfite.

A pharmaceutical composition of the invention as used herein relates to a combination of components/agents/compounds/drug/constituents.

Components/agents/compounds/drug/constituents as used herein are for example H₂-blockers, anti-inflammatory agents, cytotoxic agents, levamisole, retinoids, NFkB inhibitors, agents that enhance the intracellular accumulation of NADH + H⁺, poly-alcohols, inhibitor of pro-angiogenic growth factor(s) or MMP inhibitors.

The term "container" as used herein refers to any receptacle capable of holding at least one component of a pharmaceutical composition of the invention. Such a container may be any jar, vial or box known to a person skilled in the art and may be made of any material suitable for the components contained therein and additionally suitable for short or long term storage under any kind of temperature.

The present invention further provides a formulation consisting of an aqueous or oily suspension or solution comprising a pharmaceutical composition of the invention.

In one embodiment, the formulation is formulated for oral administration. Such oral administration may allow for treatment to take place, for example, at the patient's home.

When a formulation of the subject invention comprises sulfasalazine, sulfasalazine may be dissolved using carbonate salts. Such a carbonate salt can be any carbonate salt such as sodium carbonate or sodium bicarbonate.

- 11 -

In a further embodiment of the present invention, the formulation further comprises a flavoring agent (e.g. menthol, anethol and/or salt). In another embodiment of the present invention, part of the constituents of the aqueous or oily suspension or solution of the formulation may be supplied in a dry form and reconstituted (e.g. solubilized) prior to oral administration.

In one embodiment of the present invention compositions may be provided as sustained release or timed release formulations. The carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. Micro-encapsulation may also be used. The timed release formulation can provide a pharmaceutical composition of immediate and pulsed release throughout the day. The diluent is selected so as not to affect the biological activity of a pharmaceutical composition of the invention. Examples of such diluents are distilled water, physiological saline, Ringer's solution, dextrose solution, and Hank's solution.

A pharmaceutical composition or formulation of the subject invention may include carriers, adjuvants and emulsifiers such as poloxamers, or nontoxic, non-therapeutic, non-immunogenic stabilizers and the like. Effective amounts of such diluent or carrier will be those amounts which are effective to obtain a pharmaceutically acceptable formulation in terms of solubility of components, biological activity, and the like.

In one embodiment, the formulations include a controlled- release device or composition where one or several of the components comprised in a pharmaceutical composition of the invention are being released in a delayed fashion. Such formulation may be in the form of a tablet (or a pill) which releases different doses of components comprised in a pharmaceutical composition of the invention, in different time intervals after being administered orally.

A pharmaceutical composition of the invention may be formulated in a solid, semi-solid, or liquid form such as, e.g. suspensions, aerosols, or the like or any other formulation known to a person skilled in the art. In one embodiment, the compositions

- 12 -

are administered in unit dosage forms suitable for single administration of precise dosage amounts. The compositions may also include, depending on the formulation desired, pharmaceutically-acceptable carriers as defined above.

5 In one embodiment of the present invention, a pharmaceutical composition of the invention may be administered in a single dosage form comprising all the components together.

In another embodiment, at least one component of a pharmaceutical composition of the invention may be separately administered, simultaneously or sequentially.

10 In yet another embodiment, a pharmaceutical composition of the invention may be administered via a kit or a system comprising at least one component of a pharmaceutical composition of the invention in a separate container.

The term "*administered sequentially*" refers to ordered and successive administration of a pharmaceutical composition of the invention or their components comprised in separate containers. Said sequential administration may be 1, 2 or 3 days
15 apart. Thus, the present invention further provides a kit comprising:

- a first container comprising at least one component of a pharmaceutical composition of the invention;

- a second container comprising at least one component of a pharmaceutical composition of the invention; and instructions for administration of said containers.

20 For example, instructions may indicate administration of a first container on non-consecutive days and for administration of a second container daily.

In a further embodiment, components of a pharmaceutical composition of the invention may be comprised in multiple, i.e. more than two, containers.

25 In one embodiment, the components of a pharmaceutical composition of the invention in the first and second container are the same. In another embodiment the components of a pharmaceutical composition of the subject invention in the first and second container are not the same. For ease of storage and administration, compatible

- 13 -

components of a pharmaceutical composition of the invention may be placed in one container, separated from other components of said pharmaceutical composition.

According to one embodiment of the invention each component of a pharmaceutical composition of the invention, is contained in a separate container. In
5 another embodiment, all components for administration on a particular day are combined and stored in one container for ease of use and storage. If necessary for stability purposes, the container may be stored frozen (-20°C) and thawed before administration, e.g., by placing in a refrigerator ($4-8^{\circ}\text{C}$) one or two days before administration.

In one embodiment of the present invention, a kit comprises at least one vial of
10 H₂-blocker, at least one vial of an anti-inflammatory agent, at least one vial of a cytotoxic agent and, optionally, at least one vial of the following: levamisole, a retinoid, an NF κ B inhibitor, an agent which increases intracellular accumulation of NADH + H⁺, an inhibitor of a pro-angiogenic factor(s), an MMP inhibitor and a pharmaceutical carrier. The kit may contain instructions describing their use in administration which may be
15 simultaneous or sequential.

Experiments conducted by the inventors of the present invention showed (Example 2 and Figure 2) that neither the H₂-blocker (cimetidine) alone, nor levamisole alone demonstrated any significant anti-cancer activity. However, it was surprisingly found by the inventors that the combination of cimetidine and levamisole with a cytotoxic
20 agent, at least one anti-inflammatory agent and optionally at least one of an NF κ B inhibitor, a retinoid, an agent that enhance the intracellular accumulation of NADH + H⁺, a poly-alcohol, an inhibitor of pro-angiogenic growth factor(s) and an MMP inhibitor resulted in an enhanced anti-tumor effect thereby yielding a powerful anti-cancer therapy.

Thus, the present invention provides a method of inhibiting cancer in a mammal
25 comprising administering to the mammal a pharmaceutical composition of the invention.

The present invention further provides a method of inhibiting cancer in a mammal comprising administering to the mammal a formulation of the present invention.

The term "*cancer*" as referred to in the present invention relates to a neoplastic

- 14 -

disease which is characterized by abnormal and uncontrolled cell division causing malignant growth or tumor. Cancer cells, unlike benign tumor cells, exhibit the properties of invasion and metastasis and are highly anaplastic. Cancer includes the two broad categories of carcinoma and sarcoma. In one embodiment of the present invention the cancer is a solid tumor or tumor metastasis. In a further embodiment of the present invention, said cancer may be selected from, however not limited to, the group consisting of lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), prostate cancer including the advanced disease, hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, glioblastoma, benign tumor of the skin (e.g. keratoacanthomas), breast carcinoma (e.g. advanced breast cancer), kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

The term "*inhibiting cancer*" as used in the context of the present invention relates to a decrease in tumor size; decrease in rate of tumor growth; stasis of tumor size; decrease in the number of metastasis; decrease in the number of additional metastasis; decrease in invasiveness of the cancer; decrease in the rate of progression of the tumor from one stage to the next, inhibition of tumor growth in a tissue of a mammal having a malignant cancer, control of establishment of metastases, inhibition of tumor metastases formation, regression of established tumors as well as decrease in the angiogenesis induced by the cancer. The term "*inhibiting cancer*" can also refer to prophylaxis such as prevention as cancer reoccurs after previous treatment (including surgical removal) and prevention of cancer in an individual prone (genetically, due to life style, chronic inflammation and so forth) to develop cancer.

The term "*administering*" or its other lingual forms as used in the context of the present invention relates to the path by which a pharmaceutically active component, a

- 15 -

drug, fluid or other substance is brought into contact with the body. The pharmaceutical composition is transported from the site of entry to the part of the body where its action is desired to take place. According to one embodiment of the present invention, said administering may be achieved via any medically acceptable means suitable for a pharmaceutical composition of the invention or any component thereof, including oral, rectal, vaginal, nasal, topical, transdermal, or parenteral (including subcutaneous, intramuscular, intrasynovial, intraperitoneal, intradermal and intravenous) administration.

A pharmaceutical composition of the present invention or each component thereof can thus be administered by any means known in the art, such as oral (including buccal and sublingual), rectal, vaginal, nasal, topical, transdermal, or parenteral (including subcutaneous, intramuscular, intravenous, intrasynovial, intraperitoneal and intradermal) administration.

Pharmaceutical compositions, methods and systems of the present invention may be used either alone, or in conjunction with other cancer treatment methods known to those of skill in the art. Such methods may include, but are not limited to chemotherapy, radiation therapy or surgery. The administration of a pharmaceutical composition of the present invention may be conducted before, during or after other cancer therapies. In addition, a pharmaceutical composition of the present invention may be administered concurrently with other cancer treatments known to those of skill in the art.

Typically, oral administration requires a higher dose than intravenous administration. Thus, the administration route will depend upon the situation: the skilled artisan must determine which form of administration is best in a particular case, balancing dose needed versus the number of times per month administration is necessary.

In one embodiment the components of a pharmaceutical composition of the invention are administered using the normal dose of each component as known to a person skilled in the art.

In another embodiment the components of a pharmaceutical composition of the invention are administered using a lower dose than the dose known in the art, of one or more component. For example, when administering a cytotoxic agent, in order to reduce

- 16 -

side effects, it is possible to use a lower dose than used when administered as a single cytotoxic agent -typically 75% or less of the individual amount, more specifically 50% or less, still more specifically 40% or less.

In particular, the agent that enhances intracellular accumulation of $\text{NADH} + \text{H}^+$ (i.e. polyol) is administered at a dose of 5g to 100g per day, more specifically at a dose of 10g to 50g per day.

Components comprised in a pharmaceutical composition of the present invention may be administered in dosages which may be found appropriate by a clinician, such as those described for individual components in the Physicians Desk Reference (PDR). Non limiting examples of suitable dosages of the components of a pharmaceutical composition of the invention include:

- 50 to 400 mg per day of levamisole, more specifically 100 to 300 mg per day of levamisole.

- 200 to 4,000 mg per day of cimetidine, more specifically, 400 to 2,000 mg per day of Cimetidine.

- 0.1-50 mg/kg of cyclophosphamide, more specifically 0.2-20 mg/kg of cyclophosphamide.

- 50 to 400 per day of diclofenac, more specifically, 100 to 300 mg per day of diclofenac.

- 50 to 5,000 mg per day of sulfasalazine, more specifically 300 to 3,000 mg per day of sulfasalazine.

- 1 to 10 mg per day, of rapamycin.

- 10 to 100 mg per day of all-trans-retinoic acid (ATRA).

In one embodiment, a dosage of 0.1-50 mg/kg of cyclophosphamide, may be administered per day, twice a week or once a week. In a further embodiment, a dosage of 0.2-20 mg/kg of cyclophosphamide, may be administered per day, twice a week or once a week.

In therapeutic applications, the dosages and administration schedule of

- 17 -

components of a pharmaceutical composition of the invention may vary depending on the component, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose and administration
5 scheduled should be sufficient to result in slowing and/or regressing, the growth of the tumor(s) and may also cause complete regression of the cancer. In some cases, regression may be monitored via direct imaging (e.g. MRI) or by a decrease in blood levels of tumor specific markers. An effective amount of the pharmaceutical composition is that which provides a medical benefit as noted by the clinician or other qualified observer.
10 Regression of a tumor in a patient is typically measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Complete regression is also indicated by failure of tumors to reoccur after treatment has stopped. The present invention allows for the administration of a pharmaceutical composition of the present invention, either prophylactically or therapeutically or in the context of adjuvant or neo-
15 adjuvant treatment.

When provided prophylactically, a pharmaceutical composition of the invention may be administered in advance of any symptom. Prophylactic administration of pharmaceutical compositions may serve to prevent or inhibit cancer. A pharmaceutical composition of the invention may prophylactically be administered to a patient with, for
20 example, a family history of cancer. The risk for developing cancer may be determined by measuring levels of cancer marker proteins in the biological fluids (i.e. blood, urine) of a patient or by genetic markers. Alternatively, administration of a pharmaceutical composition of the invention may be administered to a patient with rising cancer marker protein levels. Such markers include, for example, rising PSA, CEA, thymosin β -15,
25 thymosin β -16, calcitonin, and matrix metalloproteinase (MMP). When provided prophylactically, the dose of a pharmaceutical composition of the invention may be reduced to the appropriate prophylactic dosage.

When provided therapeutically, a pharmaceutical composition of the invention may be administered at (or after) the onset of a symptom or indication of a cancer. Thus,
30 a pharmaceutical composition of the present invention may be provided either prior to the anticipated tumor growth at a site or after the malignant growth has begun at a site.

- 18 -

The term "*mammal*" as used in the context of the present invention relates to warm blooded vertebrate animals characterized by the presence of mammary glands, which produce milk in females for the nourishment of young, and in addition are covered with hair or fur. In one embodiment, said mammal may be selected from the group
5 consisting of a human, a cat, a dog and a horse.

The present invention further provides a system for the treatment or prevention of cancer comprising multiple containers, each container comprising at least one component of a pharmaceutical composition of the invention, to be administered on a scheduled day, the system comprising sufficient containers for at least one day of
10 treatment. In another embodiment, the system may comprise sufficient containers for at least 7 days of treatment.

In a specific aspect of the present invention there is provided a system for treating cancer comprising:

- a first container comprising 25-100 ml aqueous solution of 0-60% xylitol
15 comprising: cyclophosphamide in the range of 200-600mg ; diclofenac in the range of 100-300mg; levamisole in the range of 0-200mg; cimetidine in the range of 400-2,000mg; sulfasalazine in the range of 100-1,000mg or rapamycin in the range of 1-10 mg; and

- a second container comprising 25-100ml aqueous solution of 0-60%
20 xylitol comprising: cimetidine in the range of 400-2,000mg ; sulfasalazine in the range of 500-4,000mg or rapamycin in the range of 1-10 mg; optionally levamisole in the range of 100-500mg.

In another specific aspect of the present invention there is provided a system for treating cancer comprising:

25 - a first container comprising 25-100 ml aqueous solution of 0-60% xylitol comprising: cyclophosphamide in the range of 200-600mg; diclofenac in the range of 100-300mg; cimetidine in the range of 200-2,000mg; sulfasalazine in the range of 100-1,000mg or rapamycin 1-10 mg; and

- 19 -

- a second container comprising 25-100 ml aqueous solution of 0-60% xylitol comprising: cimetidine in the range of 200-2,000mg; sulfasalazine in the range of 300-4,000mg or rapamycin 1-10 mg.

5 In yet another specific aspect of the present invention there is provided a system for treating cancer comprising:

- a first container comprising 25-100 ml aqueous solution of 0-60% xylitol comprising: cyclophosphamide in the range of 200-600mg; diclofenac in the range of 100-300mg; cimetidine in the range of 400-2,000mg; ATRA in the range of 10-1,00mg; and

10 - a second container comprising 25-100 ml aqueous solution of 0-60% xylitol comprising: cimetidine in the range of 400-2,000mg; ATRA in the range of 10-100mg.

In a further embodiment of the present invention there is provided a system having at least two vials for sequential administration. The system comprises:

15 - a first container (herein referred to as a "*cytotoxic container*") comprising at least one anti-inflammatory agent, a cytotoxic agent, an H2-blocker, optionally a poly-alcohol and a redox quinone, and a pharmaceutically acceptable carrier ; and

- a separate second container (herein referred to as a "*non cytotoxic container*") comprising a H2-blocker and, optionally at least one of the following
20 Levamisole, an NFkB inhibitor, a redox quinone, a retinoid, a poly-alcohol, an inhibitor of pro-angiogenic growth factor(s), a MMP inhibitor and a pharmaceutically acceptable carrier; the system may further comprise instructions for the administration of the components in the containers.

25 In yet a further aspect, the invention provides a system for treating cancer comprising:

- a container comprising at least one anti-inflammatory agent, a cytotoxic agent, and an H2-blocker, and optionally an NFkB inhibitor, a retinoid, a redox quinone, a poly-alcohol, and a pharmaceutically acceptable carrier; and

- 20 -

- a container comprising an H2-blocker and, optionally, Levamisole, an NFkB inhibitor, a retinoid, a redox quinone, a poly-alcohol, an inhibitor of pro-angiogenic growth factor(s), a MMP inhibitor and a pharmaceutically acceptable carrier.

A system of the present invention and its use in the treatment of cancer allows for a 7 day cycle of administration of at least one of the above components of a pharmaceutical composition of the invention. This cycle may include administration of at least one component of a pharmaceutical composition of the invention on non-consecutive days, while an agent that enhances intracellular accumulation of NADH + H⁺ may be administered daily during the rest of the 7 day cycle.

For instance, such a cycle may include twice a week administration of at least one component of a pharmaceutical composition of the invention on non-consecutive days while an agent that enhances intracellular accumulation of NADH + H⁺ may be administered daily during the rest of the 7 day cycle.

In one embodiment of the present invention, the system further comprises instructions to administer a first container on Days 1 and 4 of a 7 day cycle of treatment and administer a second container on Days 2, 3, 5, 6 and 7 of the cycle of treatment.

It is understood that the foregoing detailed description and the following examples are illustrative only and are not to be taken as limitations upon the scope of the invention. Various changes and modifications to the disclosed embodiments, which will be apparent to a person versed in the art, may be made without departing from the spirit and scope of the present invention. Further, all patents, patent applications, and publications cited herein are incorporated herein by reference.

In the following exemplary embodiments of the present invention, different pharmaceutical compositions of the invention were tested *in vivo* for the purpose of suppression of tumor growth in mice. The control group received a vehicle containing only non-active ingredients which was compared to groups which received pharmaceutical compositions comprising different active ingredients as described in detail below.

The following description depicts the experimental procedures performed for

- 21 -

the *in vivo* examples detailed herein below:

(a) Inoculation

3.5x10⁵ cells of mouse mammary carcinoma (EMT₆/CTX) were injected subcutaneously in to 7-8 week-old mice of the CB6F1 strain (a cross between Balbc and C57bl), in the center of their backs. The mice were then marked and divided into groups. Typically, each group consisted of 7 to 8 mice.

(b) Tumor measurement

The tumor size was measured twice a week and plotted in a graph. The formula used for assessing the 3 dimensional size of the tumor was: length x width x width x 0.52. The width measurement was also used as an indication for tumor height, and the 0.52 is a normalizing factor.

(c) Injections

Mice were injected with a specified pharmaceutical composition, 6 days a week. Injection volume was 0.05mL per 10g body weight (25g mice received 0.125mL). All injections were performed intraperitoneally.

(d) Treatment regimen

The week was divided into two treatment types, cytotoxic treatment and non-cytotoxic treatment days according to the corresponding composition.

Treatment was initiated once small tumors were visible on the majority of mice (approximately day 5 or 6 after inoculation). The first treatment was cytotoxic and marked as day 1 of the week (D1).

Cytotoxic treatment was administered on day 1 and 4 of each week (D1 and D4 respectively). Non-cytotoxic treatment was given on days 2, 3, 5 and 6 (D2, D3, D5 and D6 respectively). No treatment was given on the 7th day. The control group was administered the vehicle every day.

- 22 -

(e) Pharmaceutical composition:

Non-cytotoxic treatment comprised the following: xylitol – 60% and either cimetidine and/or levamisole and/or sulfasalazine and/or menadione (in Examples 2 and 3 only) and/or no active ingredient (=control), according to the experimental design
5 described in the table of the corresponding example.

For the cytotoxic treatment, the following components were added to the previously described (non-cytotoxic) pharmaceutical composition: diclofenac sodium – 30 mg/Kg/day, cyclophosphamide (CTX) – 60 mg/Kg/day, according to the experimental composition described in the table of the corresponding example.

10 All components mentioned above were delivered in a vehicle containing Double Distilled Water (DDW), 2% Solutol HS-15 and 60% Xylitol. In experiments 1 and 7, the vehicle contained only DDW; no Xylitol was added.

The daily dosage of sulfasalazine was administered according to the experimental regimen, and ranges between 150-350 mg/Kg/day, according to the
15 experimental design described in the table of the corresponding example.

For all non-sulfasalazine containing compositions: DDW volume added was 60% of final volume of solution due to xylitol dissolving and volume increase. 60% xylitol was dissolved in preheated DDW (~60°C) and stirred until solution was clear. 98% of final solution volume was measured and 2% solutol (liquid) was added. All other
20 components were then added to the xylitol solution and stirred until solution was homogenous.

For compositions containing sulfasalazine: DDW volume added was 60% of final volume of solution due to xylitol dissolving and volume increase. In order to increase sulfasalazine solubility, the pH of the solution was brought to basic ranges
25 (pH~10.5). This was achieved by adding Na₂CO₃ to DDW to a concentration of 0.2M. sulfasalazine was then added and the pH neutralized. Solution was heated (~60°C) and 60% xylitol added. 98% of final solution volume was measured and 2% solutol (liquid) was added. All other components were then added to the xylitol solution and stirred until

- 23 -

solution was homogenous.

EXAMPLE 1:

Table 1 describes the pharmaceutical compositions administered to Groups 1 to 5:

Group\ Component & dosage	Group 1 (Control)	Group 2	Group 3	Group 4	Group 5
Vehicle	+	+	+	+	+
Cimetidine 20 mg/Kg all week		+		+	+
Sulfasalazine 150 mg/Kg on non-cytotoxic days, 50 mg/Kg on cytotoxic days		+			+
Diclofenac 30 mg/Kg on cytotoxic days		+	+	+	+
CTX 60 mg/Kg on cytotoxic days			+	+	+

Table 1: Pharmaceutical Compositions of Example 1

- 5 This experiment was conducted in order to show the contribution of either cimetidine by itself or together with sulfasalazine to the anti-tumor activity when added to the combination of CTX and diclofenac. The results are depicted in Figure 1. The pharmaceutical composition comprising cimetidine (Group 4) showed a more pronounced anti-tumor effect demonstrated by the reduction in tumor size, compared to the anti-tumor effect of the pharmaceutical compositions comprising only CTX and diclofenac (Group 3) or a composition comprising diclofenac, sulfasalazine and cymetidine (Group 2). The addition of both cimetidine and sulfasalazine to the pharmaceutical composition (Group 5), gave the most pronounced reduction in tumor size.
- 10

- 24 -

EXAMPLE 2:

Table 2 describes the pharmaceutical compositions administered to Groups 1 to 4.

Group\ Component & dosage	Group 1 (Control)	Group 2	Group 3	Group 4
Vehicle	+	+	+	+
Levamisole 12 mg/Kg on non-cytotoxic days		+		+
Cimetidine 20 mg/Kg all week			+	+

Table 2: Pharmaceutical Compositions of Example 2

The results as depicted in Figure 2, show that neither levamisole (Group 2), nor
5 cimetidine (Group 3), nor their combination (Group 4) had any significant effect on
tumor growth.

- 25 -

EXAMPLE 3:

Table 3 describes the pharmaceutical compositions administered to Groups 1 to 3:

Group\ Component & dosage	Group 1 (Control)	Group 2	Group 3
Vehicle	+	+	+
Levamisole 12 mg/Kg on non-cytotoxic days			+
Cimetidine 20 mg/Kg all week			+
Menadione 27.5 mg/Kg all week		+	+
Sulfasalazine 150 mg/Kg on non-cytotoxic days, 50 mg/Kg on cytotoxic days		+	+
Diclofenac 30 mg/Kg on cytotoxic days		+	+
CTX 60 mg/Kg on cytotoxic days		+	+

Table 3: Pharmaceutical Compositions of Example 3.

Figure 3 shows a significant reduction in tumor size upon the addition of cimetidine and levamisole to pharmaceutical compositions comprising combinations of CTX, diclofenac, sulfasalazine and menadione (Group 3 vs. Group 2, in Figure 3) (as compared to control group). A significant reduction in tumor size was observed for Group 2 and Group 3. Hence, the concomitant addition of cimetidine and levamisole enhanced the anti-tumor activity of pharmaceutical compositions comprising combinations of CTX, diclofenac, sulfasalazine and menadione.

- 26 -

EXAMPLE 4:

Table 4 describes the pharmaceutical compositions administered to Groups 1 to 3:

Group\ Component & dosage	Group 1 (Control)	Group 2	Group 3
Vehicle	+	+	+
Levamisole 12 mg/Kg on non-cytotoxic days			+
Cimetidine 20 mg/Kg all week			+
Menadione 27.5 mg/Kg all week		+	+
Diclofenac 30 mg/Kg on cytotoxic days		+	+
CTX 60 mg/Kg on cytotoxic days		+	+

Table 4: Pharmaceutical Compositions of Example 4

The pharmaceutical compositions of this experiment are similar to the compositions of Experiment 2, with the absence of sulfasalazine in the combination of either cytotoxic or non-cytotoxic treatments. The results are depicted in Figure 4. Reduction in tumor size was achieved upon addition of cimetidine and levamisole to pharmaceutical compositions comprising combinations of CTX, diclofenac and menadione (as compared to control group).

- 27 -

EXAMPLE 5:

Table 5 describes the pharmaceutical compositions administered to Groups 1 to 4:

Group\ Component & dosage	Group 1 (Control)	Group 2	Group 3	Group 4
Vehicle	+	+	+	+
Levamisole 12 mg/Kg on non-cytotoxic days			+	+
Cimetidine 20 mg/Kg all week		+		+
Diclofenac 30 mg/Kg on cytotoxic days		+	+	+
CTX 60 mg/Kg on cytotoxic days		+	+	+

Table 5: Pharmaceutical Compositions of Example 5

This experiment was conducted in order to show the contribution of either
 5 cimetidine or levamisole or their combination to the anti-tumor activity when added to
 CTX and diclofenac. The results are depicted in Figure 5. The pharmaceutical
 composition comprising cimetidine (Group 2) showed a more pronounced anti-tumor
 effect reducing the tumor size, compared to pharmaceutical compositions comprising
 levamisole (Group 3). The addition of both cimetidine and levamisole to the
 10 pharmaceutical composition (Group 4), gave the most pronounced tumor size reduction.

- 28 -

EXAMPLE 6:

Table 6 describes the pharmaceutical compositions administered to Groups 1 to 4:

Group\ Component & dosage	Group 1 (Control)	Group 2	Group 3	Group 4
Vehicle	+	+	+	+
Levamisole 12 mg/Kg on non-cytotoxic days				+
Cimetidine 20 mg/Kg all week			+	+
Sulfasalazine 150 mg/Kg on non-cytotoxic days, 50 mg/Kg on cytotoxic days		+	+	+
Diclofenac 30 mg/Kg on cytotoxic days		+	+	+
CTX 60 mg/Kg on cytotoxic days		+	+	+

Table 6: Pharmaceutical Compositions of Example 6

This experiment was conducted in order to show the contribution of either
 5 cimetidine by itself or together with levamisole to the anti-tumor activity when added to
 the combination of CTX, diclofenac and sulfasalazine. The results are depicted in Figure
 6. The pharmaceutical composition comprising cimetidine (Group 3) showed
 significantly more pronounced anti-tumor effect reducing the tumor size, compared to the
 same pharmaceutical compositions but without cimetidine (Group 2). The addition of
 10 both cimetidine and levamisole to the pharmaceutical composition (Group 4), gave the
 most pronounced reduction in tumor size.

- 29 -

EXAMPLE 7:

Table 7 describes the pharmaceutical compositions administered to Groups 1 to 4:

Group\ Component & dosage	Group 1 (Control)	Group 2	Group 3	Group 4
Vehicle	+	+	+	+
All Trans Retinoic acid (ATRA) 30 mg/Kg on non-cytotoxic days, 60 mg/Kg on cytotoxic days				+
Cimetidine 20 mg/Kg all week			+	+
Sulfasalazine 150 mg/Kg on non-cytotoxic days, 50 mg/Kg on cytotoxic days			+	
Diclofenac 30 mg/Kg on cytotoxic days		+	+	+
CTX 60 mg/Kg on cytotoxic days		+	+	+

Table 7: Pharmaceutical Compositions of Example 7

This experiment was conducted in order to show the contribution of either
 5 sulfasalazine or All Trans Retinoic Acid (ATRA) to the anti-tumor activity when added
 to the combination of CTX, diclofenac and cimetidine. The results are depicted in Figure
 7. The pharmaceutical composition comprising cimetidine and sulfasalazine (Group 3)
 showed more pronounced anti-tumor effect reducing the tumor size, compared to
 pharmaceutical compositions comprising CTX and diclofenac (Group 2). While the
 10 replacement of sulfasalazine by ATRA (Group 4), gave the most pronounced reduction in
 tumor size.

- 30 -

EXAMPLE 8:*(a) Tested Subject*

A female breast cancer patient with metastases at bone, lung, liver and neck, was enrolled into treatment with a pharmaceutical composition of the invention. Treatment
5 was commenced after unsatisfactory results with other hormone therapy treatments and also other state-of-the-art chemotherapy treatment comprising Vinorelbine and Capcitabine. Two months prior to treatment with the composition, the tumor size increased by 25%.

(b) Monitoring

10 Progression of disease was monitored every 6-8 weeks by a CT measurement of patient's tumor size.

(c) Pharmaceutical composition and administration thereof

The product was packed in 2 types of individual color-coded vials:

- Blue capped vials containing cyclophosphamide, cimetidine, sulfasalazine
15 and diclofenac sodium in the amounts specified in the Table 8 below.
- Red capped vials containing sulfasalazine and cimetidine, in the amounts specified in Table 8 below.

Weekly doses were packed in kits (Styrofoam containers) that include 7 vials corresponding to a daily dose, and labeled according to the administration day: Two blue
20 capped vials (days 1 and 4), and five red capped vials (days 2, 3, 5, 6 and 7).

The therapeutic product was supplied in 3 set doses: 25ml, 37.5ml, and 50ml. The patient received the 25 ml vials during the 1st week of treatment, the 37.5 ml vials during the 2nd week, and from the 3rd week and on, she received the full dose of 50 ml.

The weekly treatment cycle began on Sunday. The Blue capped vials were
25 administered orally on Sunday and Wednesday while the Red capped vials were

- 31 -

administered on Monday, Tuesday, Thursday, Friday and Saturday.

Component	25ml vials	37.5ml vials	50ml vials
Blue Capped Vials			
Cyclophosphamide	200mg	300mg	400mg
Cimetidine	200mg	300mg	400mg
Sulfasalazine	150mg	225mg	300mg
Diclofenac Sodium	100mg	150mg	200mg
Red Capped Vials			
Sulfasalazine	450mg	675mg	900mg
Cimetidine	200mg	300mg	400mg

Table 8: Pharmaceutical Composition of Example 8

(d) Results

After 3 months of treatment, there was no noted progression of the disease (i.e. 0% change in tumor-size), while after 5 months with the above treatment, the tumor grew only by 1% (as opposed to 25% during 2 months prior to treatment). These results demonstrate that the treatment according to the present invention causes a dramatic decrease in tumor growth.

CLAIMS:

1. A pharmaceutical composition comprising: an H₂-blocker, at least one non-steroidal anti-inflammatory agent, a cytotoxic agent and a pharmaceutically acceptable carrier.
2. The pharmaceutical composition of claim 1, wherein the composition further comprises levamisol.
3. The pharmaceutical composition of any one of claims 1 and 2, wherein the composition further comprises an NFkB inhibitor.
4. The pharmaceutical composition of any one of claims 1 to 3, wherein the composition further comprises at least one agent that enhances intracellular accumulation of NADH + H⁺.
5. The pharmaceutical composition of any one of claims 1 to 4, wherein the composition further comprises an inhibitor of a matrix metalloproteinase.
6. The pharmaceutical composition of any one of claims 1 to 5, wherein the composition further comprises an inhibitor of a pro-angiogenic factor.
7. The pharmaceutical composition of any one of claims 1 to 6, wherein the composition further comprises a redox quinone.
8. The pharmaceutical composition of claim 7, wherein the redox quinone is Vitamin K₃.
9. The pharmaceutical composition of claim 8, wherein Vitamin K₃ is selected from a group consisting of menadione and menadione sodiumbisulfite.
10. The pharmaceutical composition of any one of claims 1 to 9, wherein the cytotoxic agent is selected from the group consisting of: cyclophosphamide, ifosfamide, cytarabine, 6-mercaptopurine, 6-thioguanine, vincristine, doxorubicin, daunorubicin, chlorambucil, carmustine, vinblastine, methotrexate, mitoxantrone, and paclitaxel or their pharmaceutically acceptable salts.
11. The pharmaceutical composition of claim 10, wherein the cytotoxic agent is cyclophosphamide or ifosfamide.
12. The pharmaceutical composition of claim 1, wherein the non-steroidal anti-inflammatory agent is selected from a group consisting of COX-1 and COX-2 inhibitors.

13. The pharmaceutical composition of claim 12, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of diclofenac, piroxicam and indomethacin.
14. The pharmaceutical composition of claim 4, wherein the agent that enhances intracellular accumulation of $\text{NADH} + \text{H}^+$ is a poly-alcohol.
15. The pharmaceutical composition of claim 14, wherein the poly-alcohol is selected from the group consisting of xylitol, mannitol, sorbitol, arabinol, and iditol.
16. The pharmaceutical composition of claim 15, wherein the poly-alcohol is xylitol.
17. The pharmaceutical composition of any one of claims 1 to 16, wherein the H_2 -blocker is selected from the group consisting of cimetidine, ranitidine, famotidine and nizatidine.
18. The pharmaceutical composition of any one of claims 1 to 17 wherein the composition further comprises a retinoid.
19. The pharmaceutical composition of claim 18, wherein the retinoid is all-trans-retinoic-acid (ATRA).
20. The pharmaceutical composition of claim 3 wherein the NFkB inhibitor is sulfasalazine or rapamycin.
21. A formulation consisting of an aqueous suspension or solution comprising the pharmaceutical composition of any one of claims 1 to 20.
22. A formulation consisting of an oily suspension comprising the pharmaceutical composition of any one of claims 1 to 20.
23. The formulation of claim 21 or 22, wherein the formulation is adapted for oral administration.
24. The formulation of any one of claims 21 to 23 further comprising a flavoring agent.
25. The formulation of claim 21, wherein at least part of the constituents of said aqueous suspension or solution are supplied in a dry form and reconstituted to an aqueous suspension or solution prior to oral administration.
26. The formulation of any one of claims 21 to 25 wherein sulfasalazine is dissolved using carbonate salts.

27. The formulation of claim 26, wherein the carbonate salt is selected from sodium carbonate or sodium bicarbonate.
28. A kit comprising:
- a first container comprising the composition of any one of claims 1-20;
 - a second container comprising the composition of any one of claims 1-20; and
- instructions for administration.
29. The kit according to claim 28, wherein said instructions are for administration of the first container on non-consecutive days and for administration of the second container daily.
30. The pharmaceutical composition of any one of claims 1-20, for use in inhibiting cancer in a mammal.
31. The formulation of any one of claims 21-27, for use in inhibiting cancer in a mammal.
32. The pharmaceutical composition of claim 30 or the formulation of claim 31, wherein said cancer is a solid tumor or tumor metastasis.
33. The pharmaceutical composition of claim 30 or 32 or the formulation of claim 31 or 32, wherein said cancer is selected from the group consisting of lung cancer, pancreatic cancers, colon cancers, prostate cancer, hematopoietic tumors of lymphoid lineage, myeloid leukemias, thyroid follicular cancer, myelodysplastic syndrome, tumors of mesenchymal origin, melanomas, teratocarcinomas, neuroblastomas, gliomas, glioblastoma, benign tumor of the skin, breast carcinoma, kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.
34. A system for use in the treatment or prevention of cancer comprising multiple containers, each container comprising the composition of any one of claims 1-20, to be administered on a scheduled day, the system comprising sufficient containers for at least one day of treatment; and instructions for administration.
35. The system of claim 34, wherein the system comprises sufficient containers for at least 7 days of treatment.
36. The system of claim 34, wherein the composition is formulated for oral administration.
37. A system for use in the treatment of cancer comprising:

a first container comprising 25-100 ml aqueous solution of 0-60% Xylitol comprising:

Cyclophosphamide	200-600mg
Diclofenac	100-300mg
Levamisole	0-200mg
Cimetidine	400-2,000mg
Sulfasalazine	100-1,000mg or Rapamycin 1-10 mg;

and

a second container comprising 25-100 ml aqueous solution of 0-60% Xylitol comprising:

Levamisole	100-500mg
Cimetidine	400-2,000mg
Sulfasalazine	500-4,000mg or Rapamycin 1-10 mg;

and instructions for administration.

38. The system of claim 37, further comprising instructions to administer the first container twice a week on Days 1 and 4 of a weekly cycle of treatment and administer the second container five times a week on Days 2, 3, 5, 6 and 7 of a weekly cycle of treatment.

39. A system for use in the treatment of cancer comprising:

a first container comprising 25-100 ml aqueous solution of 0-60% Xylitol comprising:

Cyclophosphamide	200-600mg
Diclofenac	100-300mg
Cimetidine	200-2,000mg
Sulfasalazine	100-1,000mg or Rapamycin 1-10 mg;

and

a second container comprising 25-100 ml aqueous solution of 0-60% Xylitol comprising:

Cimetidine	200-2,000mg
Sulfasalazine	300-4,000mg or Rapamycin 1-10 mg;

and instructions for administration.

40. The system of claim 39, further comprising instructions to administer the first container twice a week on Days 1 and 4 of a weekly cycle of treatment and administer the second container five times a week on Days 2, 3, 5, 6 and 7 of a weekly cycle of

treatment.

41. A system for use in the treatment of cancer comprising:

a first container comprising 25-100 ml aqueous solution of 0-60% Xylitol comprising:

Cyclophosphamide	200-600mg
Diclofenac	100-300mg
Cimetidine	400-2,000mg
ATRA	10-100mg ; and

a second container comprising 25-100 ml aqueous solution of 0-60% Xylitol comprising:

Cimetidine	400-2,000mg
ATRA	10-100mg;

and instructions for administration.

42. The system of claim 41, further comprising instructions to administer the first container twice a week on Days 1 and 4 of a weekly cycle of treatment and administer the second container five times a week on Days 2, 3, 5, 6 and 7 of a weekly cycle of treatment.

43. A system for use in the treatment of cancer comprising:

a container comprising at least one anti-inflammatory agent, a cytotoxic agent, an H2-blocker, optionally an NFkB inhibitor, a retinoid, a redox quinone, a poly-alcohol, and a pharmaceutically acceptable carrier; and

a container comprising an H2-blocker and, optionally, Levamisole, an NFkB inhibitor, a retinoid, a redox quinone, a poly-alcohol, an inhibitor of pro-angiogenic growth factor(s), a MMP inhibitor and a pharmaceutically acceptable carrier;

and instructions for administration.

1/4

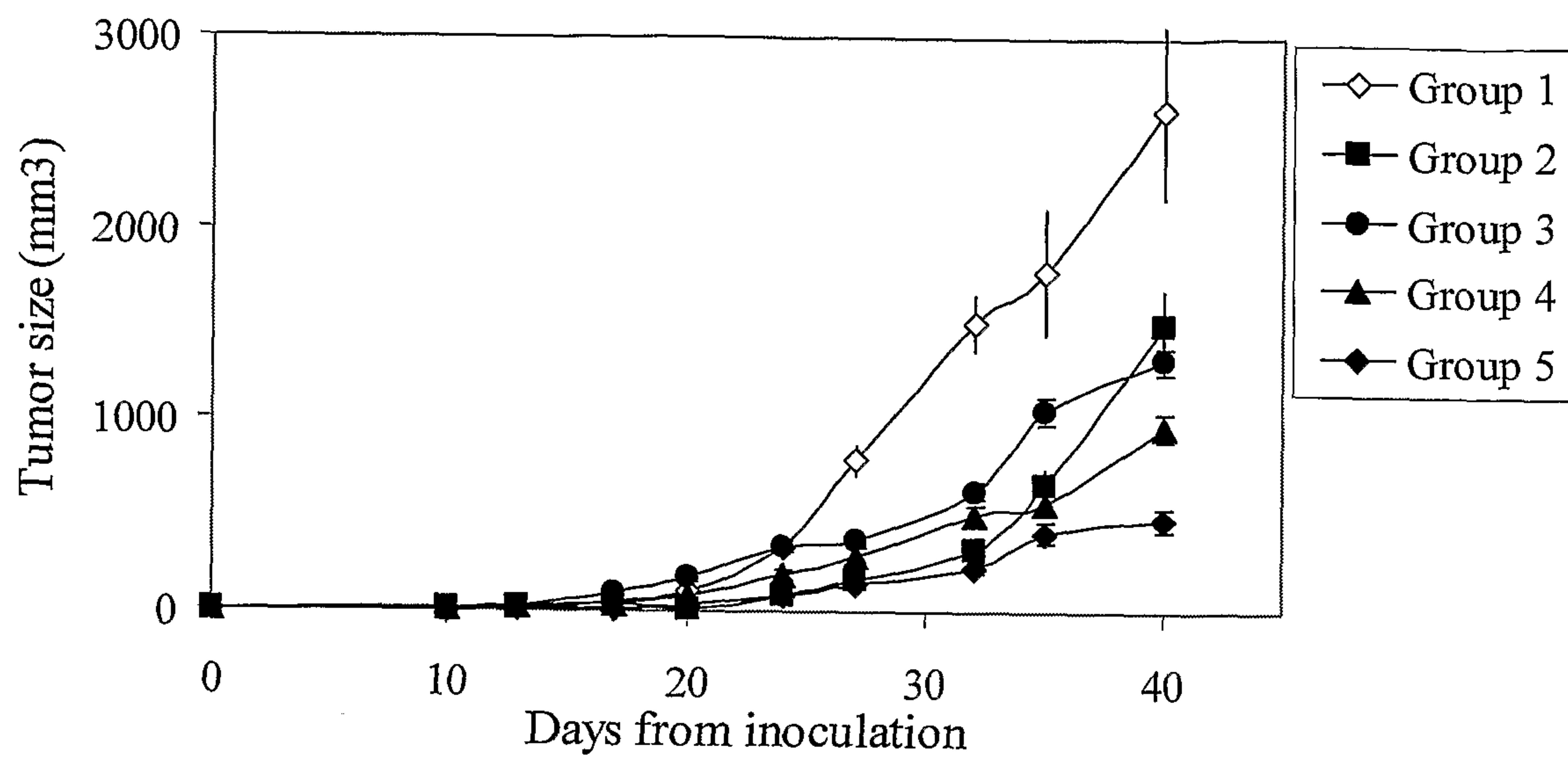


Figure 1

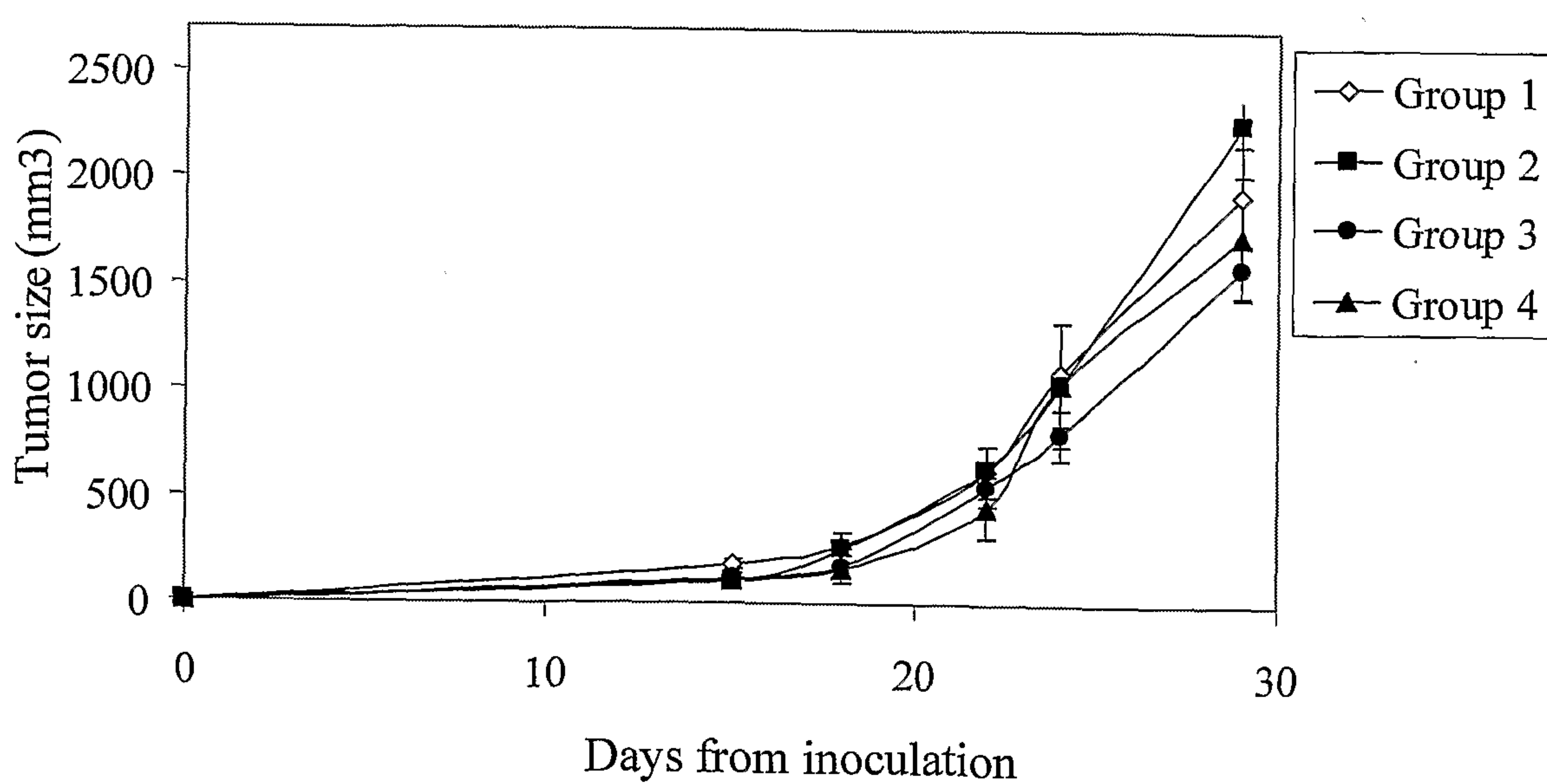


Figure 2

2/4

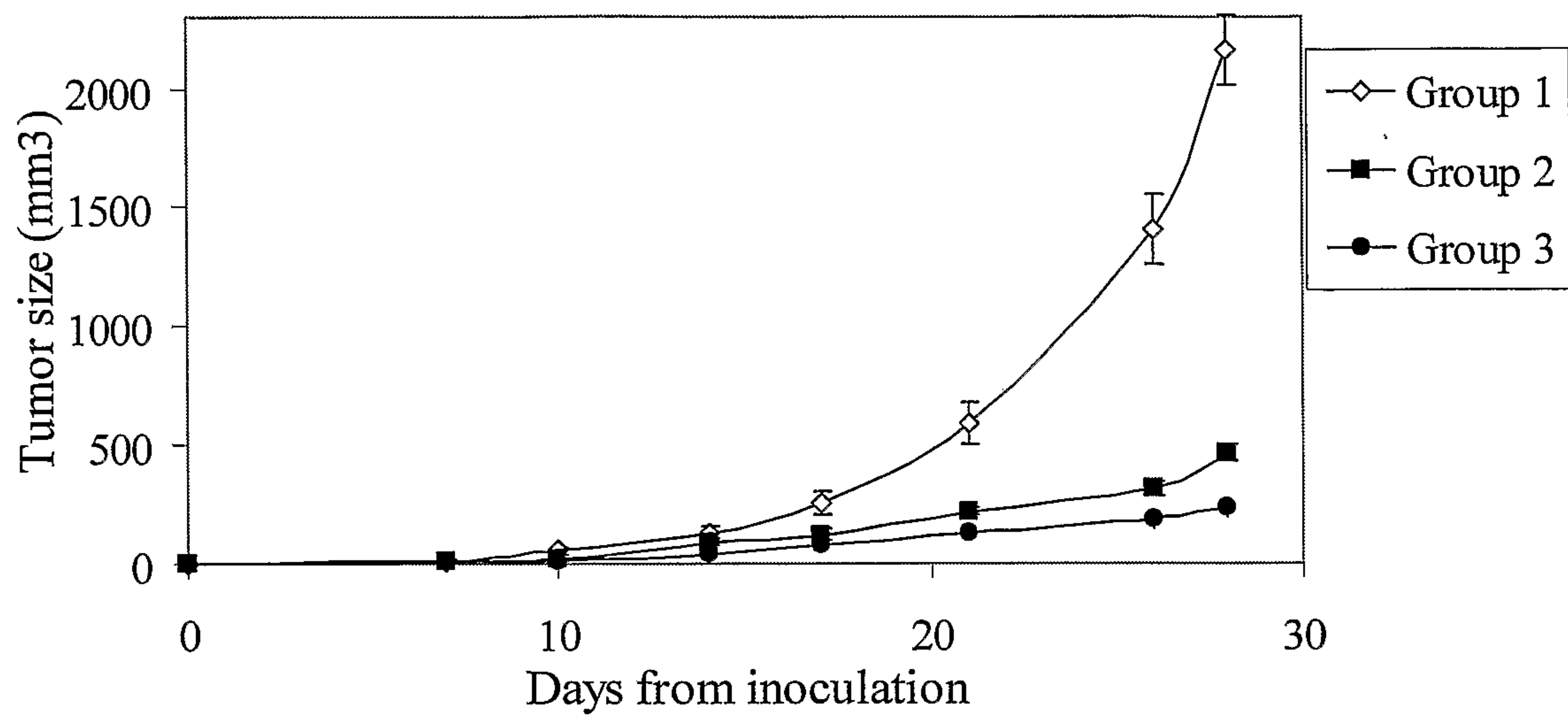


Figure 3

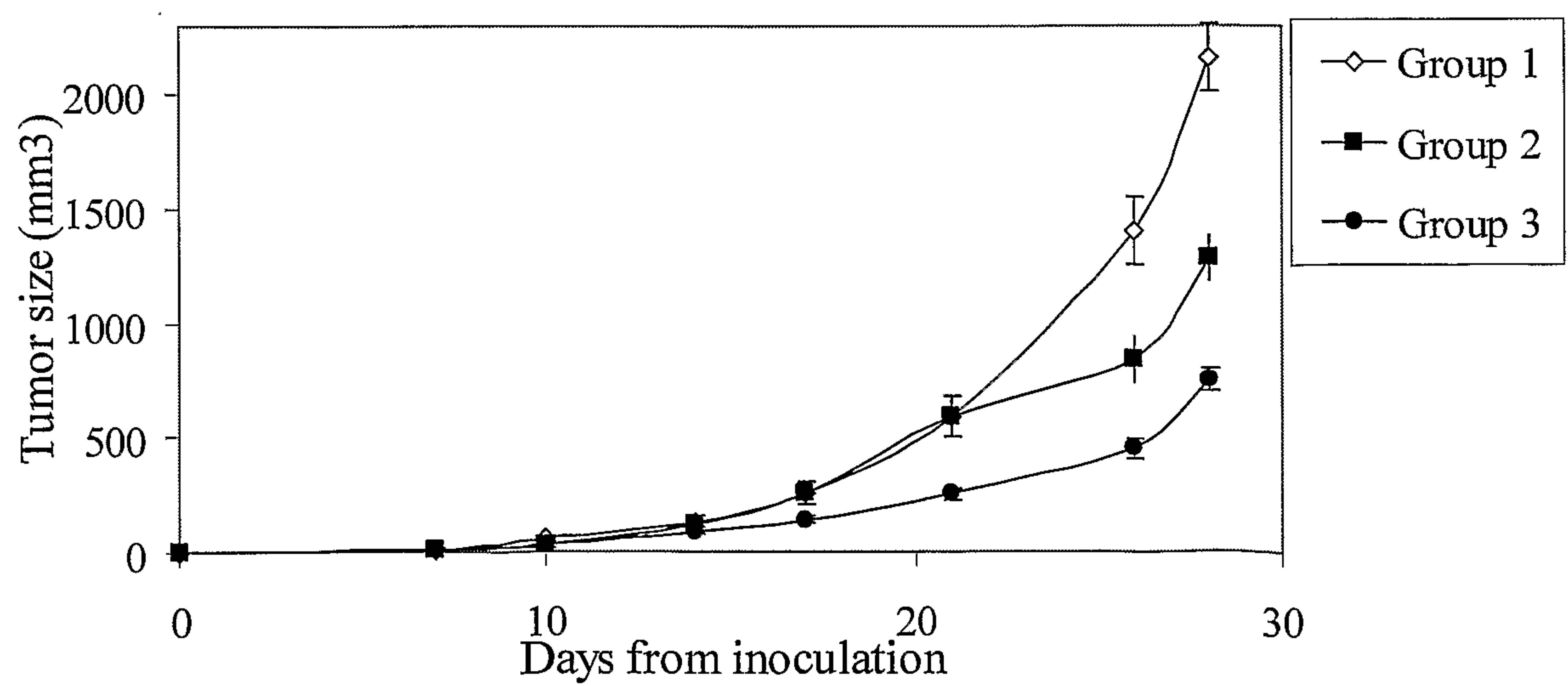


Figure 4

3/4

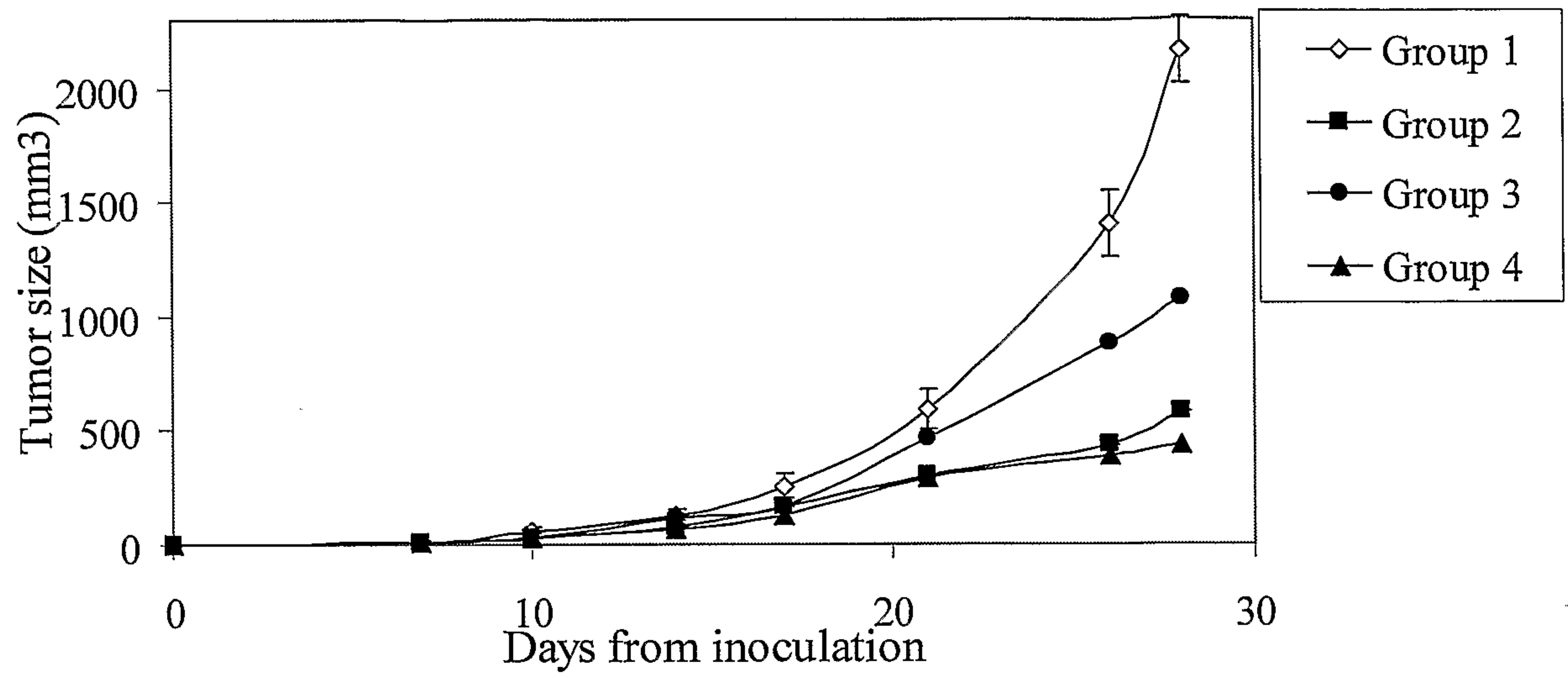


Figure 5

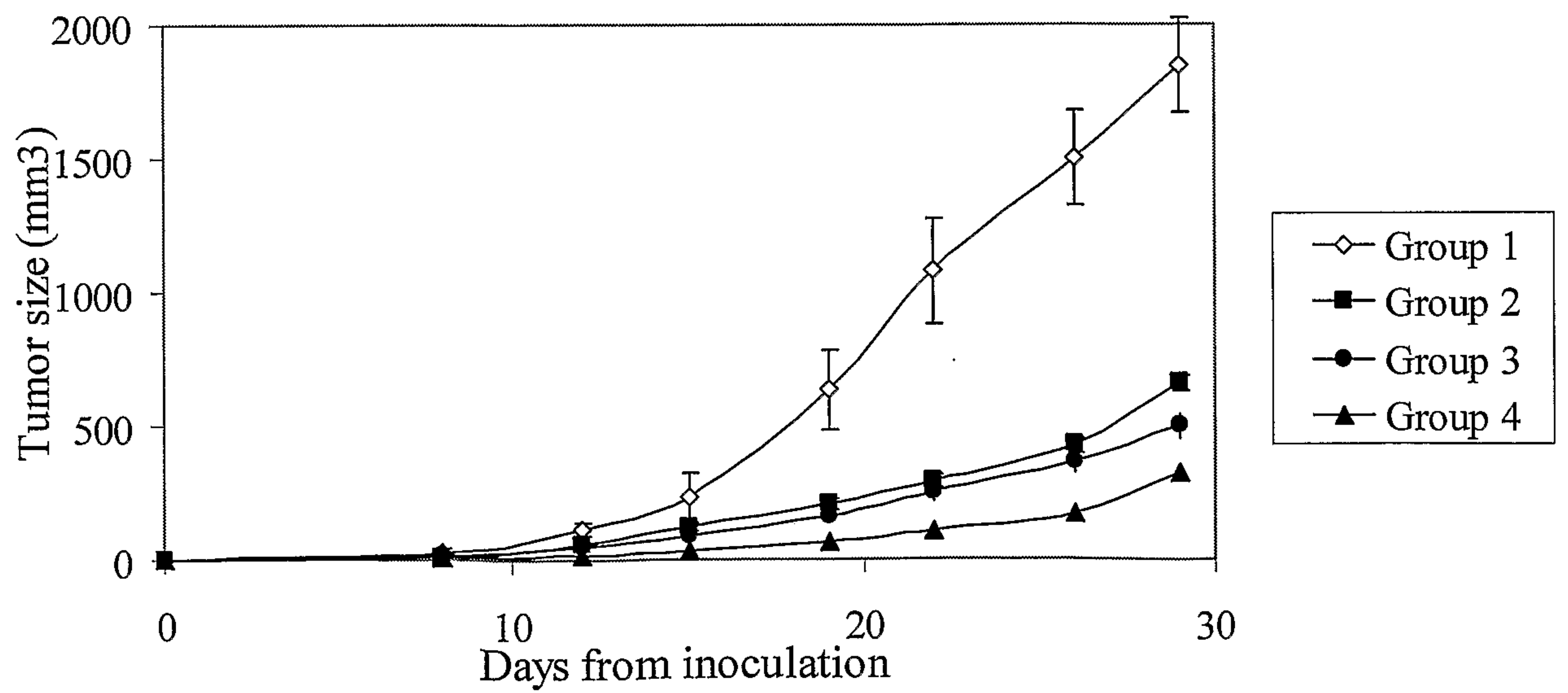


Figure 6

4/4

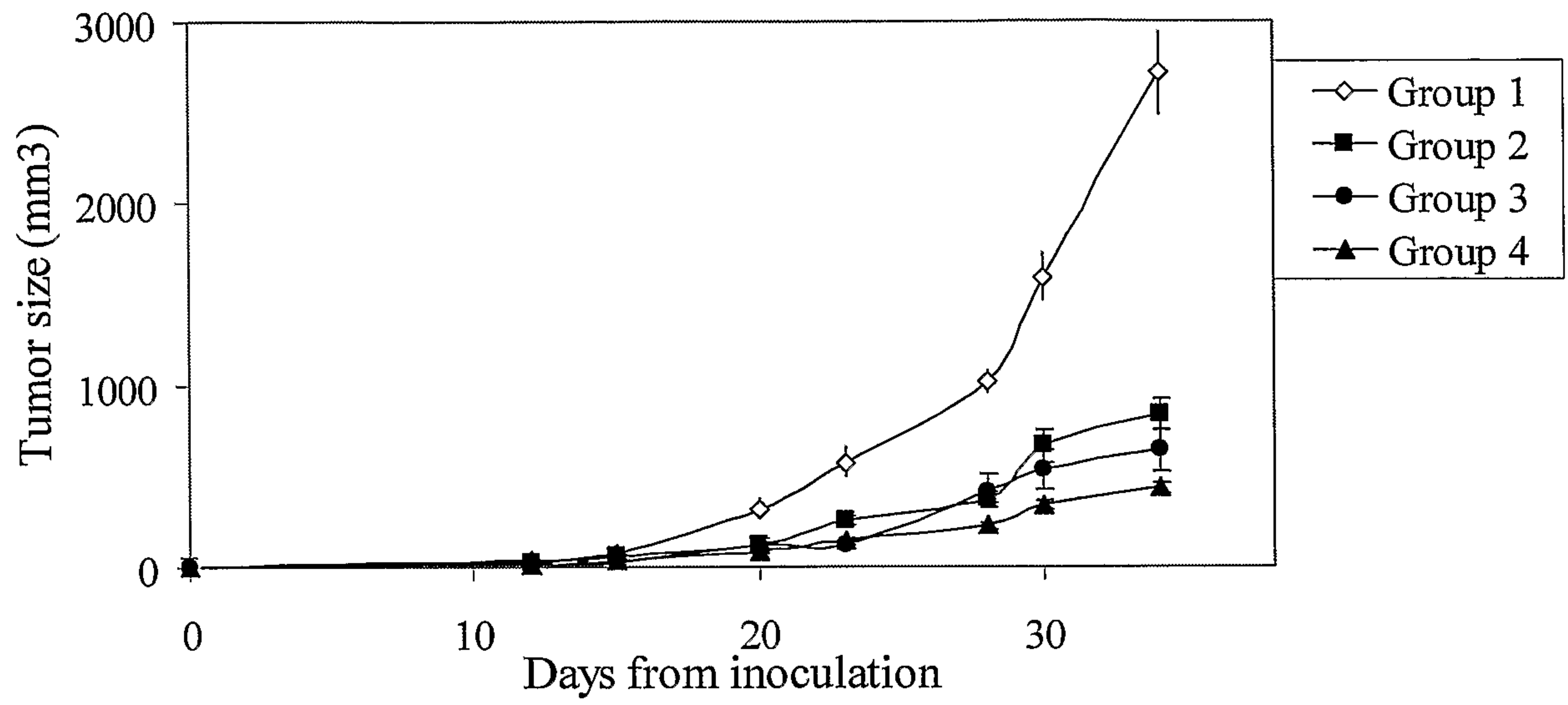


Figure 7