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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 April 2015 (09.04.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/051349 A1

(51) International Patent Classification:
A61K 9/51 (2006.01) *A61K 31/337* (2006.01)

(21) International Application Number:
PCT/US2014/059207

(22) International Filing Date:
4 October 2014 (04.10.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/961,093 4 October 2013 (04.10.2013) US

(71) Applicant: **SORRENTO THERAPEUTICS, INC.** [US/US]; 6042 Cornerstone Court West, San Diego, CA 92121 (US).

(72) Inventors: **MOTMED, Korous**; 6042 Cornerstone Court West, San Diego, CA 92121 (US). **TRIEU, Vuong**; 4003 Jim Bowie, Agoura Hills, CA 91301 (US).

(74) Agent: **OSTER, Jeffrey B.**; Sorrento Therapeutics, Inc., 6042 Cornerstone Court West, San Diego, CA 92121 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

WO 2015/051349 A1

(54) Title: TREATING METASTATIC CANCER WITH MICELLULAR PACLITAXEL

(57) Abstract: There is disclosed a method for treating peritoneal metastatic cancers comprising administering a nanoparticulate formulation of paclitaxel intraperitoneally. More specifically, there is disclosed a method for treating metastatic cancers comprising intraperitoneal or intravesicle administration a nanoparticulate formulation of paclitaxel comprising paclitaxel encapsulated in a micelle with a diblock copolymer.

TREATING METASTATIC CANCER WITH MICELLULAR PACLITAXEL

Technical Field

The present disclosure provides a method for treating peritoneal metastatic cancers comprising administering a nanoparticulate formulation of paclitaxel intraperitoneally. More specifically, the present disclosure provides a method for treating metastatic cancers comprising intraperitoneal or intravesicle administration a nanoparticulate formulation of paclitaxel comprising paclitaxel encapsulated in a micelle with a diblock copolymer.

Background

Abraxane (nab-paclitaxel) and Taxol (chremephore-solubilized paclitaxel) are paclitaxel pharmaceutical formulations. Taxol is solvent based and should be carefully administered since it is an irritant. Side effects are common although the symptoms are either one or two in most cases. The most common side effects include hair loss, peripheral neuropathy, vomiting, diarrhea, myalagia, arthralagia, low blood counts and hypersensitivity. Taxol is a first generation paclitaxel formulation in which Cremophor EL (polyoxyethylated castor oil) is mixed with paclitaxel and given as an infusion for the treatment of ovarian cancer, lung cancer, head and neck cancer, bladder cancer. Taxol has adverse side effects such as anaphylactic shock. Abraxane is paciltaxel nanoparticle encapsulated by albumin.

Abraxane (nab-paclitaxel) is used in first and second line of treatment in metastatic breast cancer. Side effects of Abraxane include bone marrow suppression (primarily neutropenia) which is dose-dependent and a dose-limiting toxicity of Abraxane. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC) and 47% of patients with non-small cell lung cancer (NSCLC).

IG-001 is a polymer bound nanoparticle paclitaxel.

Ovarian cancer is the fifth deadliest disease among American women, with more than 50% presenting with serous papillary histology. High-grade serous epithelial ovarian cancer (SEOC) is associated with intraperitoneal spreading (carcinomatosis) and distant metastases. Standard treatment is aggressive surgical resection followed by platinum-taxane chemotherapy. Platinum-resistant cancer recurs in approximately 25% of patients within 6 months, and the overall 5-year survival probability is 31%. Therefore, there is a dire need to develop new therapeutics and enhance the delivery of current effective therapeutics.

While there are cytotoxic drug compositions that are useful in the treatment of various cancers there exists a need for methods of treatment and drug administration that address metastatic cancers, particularly when there is widespread metastatic cancer in the peritoneum.

Summary

The present disclosure provides a method for treating peritoneal metastatic cancers comprising administering a nanoparticulate formulation of paclitaxel intraperitoneally. More specifically, the present disclosure provides a method for treating metastatic cancers comprising intraperitoneal or intravesicle administration a nanoparticulate formulation of paclitaxel comprising paclitaxel encapsulated in a micelle with a diblock copolymer. The present disclosure provides a method for treating metastatic cancers comprising intraperitoneal or intravesicle administeration a nanoparticulate formulation of paclitaxel comprising paclitazel encapsulated in a micelle with a diblock copolymer. More specifically, the present disclosure provides a method for administering a nanoparticulate formulation of paclitaxel comprising infusing a nanoparticulate formulation intraperitoneally at a dose of from about 15 mg/kg/day to about 60 mg/kg/day. More preferably, the intraperitoneal dose of paclitaxel is from 25 mg/kg/day to 50 mg/kg/day. Most preferably, the intraperitoneal dose of paclitaxel is from 30 mg/kg/day to 50 mg/kg/day. Preferably, the nanoparticulate formulation of paclitaxel has a particle size average of 15 nm to 40 nm.

The present disclosure provides compositions comprising cancer drugs in a micelle where the composition is stable in protein-free medium and less stable in a protein containing medium. The compositions of the present invention are conditionally stable in that they are more stable in one media than another, in particular the compositions are more stable in protein-free medium and less stable in a protein containing medium. The present disclosure provides paclitaxel compositions where the paclitaxel is contained within a micelle and where the paclitaxel composition is stable in protein-free medium and less stable in a protein containing medium. The present disclosure further provides micellular compositions where the composition comprises about 4 μg/ml to about 2000 μg/ml of paclitaxel. The present disclosure provides micellular compositions where the composition is at least 20% more stable or 50% more stable or 100% more stable in a protein-free solution than in a solution containing protein. The present disclosure provides micellular compositions where the composition is at least 20% more stable or 50% more stable or 100% more stable in a protein-free solution than nab-paclitaxel. The present disclosure provides micellular

compositions where the composition is at least 20% less stable or 50% less stable or 100% less stable in a protein containing solution such as serum than nab-paclitaxel.

The disclosure provides methods of treating patients with metastatic breast cancer by administering paclitaxel-containing micelles to patients. The disclosure provides methods of treating patients with metastatic cancer by administering paclitaxel-containing micelles to patients where the micelles are comprised of a diblock copolymer including IG-001 which is a paclitaxel-containing micelle. The present disclosure provides method of treating metastatic breast cancer wherein the amount of paclitaxel administered is at least 190mg/m^2. The present disclosure provides methods of treating metastatic breast cancer where the paclitaxel containing micelles are administered in at least 3 cycles. The present disclosure provides method of treating metastatic breast cancer where the paclitaxel containing micelles are administered from 3 cycles to 20 cycles. The present disclosure provides methods of treating metastatic breast cancer where the paclitaxel containing micelles are administered from 3 cycles to 15 cycles. The present disclosure provides method of treating metastatic breast cancer where the paclitaxel containing micelles are administered from 3 cycles to 10 cycles. The present disclosure provides method of treating metastatic breast cancer where the paclitaxel containing micelles are administered from 5 cycles to 10 cycles. The present disclosure provides method of treating metastatic breast cancer where the overall response rate is greater than 20% or greater than 30% or greater than 40% or greater than 50% or from between about 20% to about 90% or from about 25% to about 75% or from about 30% to about 60% or from 30% to about 50% or from about 30% to about 40%. The present disclosure provides method of treating metastatic breast cancer by administering paclitaxel containing micelles to the patient at least twice such that there is a first dose and a second dose. The present disclosure provides method of treating metastatic breast cancer by administering paclitaxel containing micelles to the patient at least twice such that there is a first dose and a second dose where the first dose is about 300 mg/m^2 and the second dose is about 240 mg/m^2. The present disclosure provides method of treating patients with metastatic breast cancer comprising administering paclitaxel containing micelles to the patient comprising administering a dose of paclitaxel containing micelles containing about 300 mg/m^2 pacitaxel for at least one cycle; administering a dose of paclitaxel containing micelles containing about 260 mg/m^2 pacitaxel for at least one cycle; and administering a dose of paclitaxel containing micelles containing about 190 mg/m^2 pacitaxel for at least one cycle.

Brief Description of the Figures

Figure 1 – Plot of particle size versus paclitaxel concentration for nab-paclitaxel in phosphate buffered saline (PBS) and 0.1x serum and 1x serum.

Figure 2 - Plot of particle size versus paclitaxel concentration for IG-001 in phosphate buffered saline (PBS) and 0.1x serum and 1x serum.

Figure 3 – Plot of dose proportionality curve for Taxol, nab-paclitaxel and IG-001

Figure 4 - Plot of dose limiting toxicity curve for Taxol, nab-paclitaxel and IG-001.

Figure 5 – Plot of paclitaxel concentration of delivery of 30 mg/kg bolus by Abraxane and IG-001

Figure 6A and B – Plots of paclitaxel versus time for nab-paclitaxel and IG-001 in mice.

Figure 7 – Plot of overall response rate for IG-001, Taxol and nab-paclitaxel in Phase III study of metastatic breast cancer.

Figure 8 shows the effects of the treatments in Example 5 in terms of weight gains of the mice.

Figure 9 shows that treatment with either ip IG-001 or iv ABX (nab-paclitaxel) significantly increased the median survival of mice compared to untreated control

Figure 10 shows overall survival of control and experimental groups of mice in Example 5.

Figure 11 shows Kaplan Meier curves of the survival of IG-001 (Pax) treated group (left) and nab-paclitaxel (ABX) treated group (right).

Figure 12 shows (Left) Box plots of tumor burden arbitrary scores of mice treated with ip IG-001. And (Right) dot plots of the incidence and amount of ascitic fluid accumulating in tumor-bearing mice receiving the indicated doses of IG-001. *Statistical analysis between the indicated groups was performed by Mann-Whitney non-parametric t-test. **Disease progression as a function of the indicated doses of IG-001 was analyzed by Kruskall Wallis test (non-parametric One Way ANOVA).. The incidence of ascites development was analyzed by Chi square (X^2) test, $^{\#}P<0.0001$. Ascites volume in treated mice compared to controls was analyzed by One way ANOVA and unpaired Student's t-test.

Figure 13 shows (Left) Box plots of tumor burden arbitrary scores of mice treated with iv ABX. and (Right) Dot plots of the incidence and amount of ascitic fluid accumulating in tumor-bearing mice receiving the indicated doses of ABX. *Statistical analysis between the indicated groups was performed by Mann-Whitney non-parametric t-test. **Disease progression as a function of the indicated doses of ABX was analyzed by Kruskall Wallis test (non-parametric One Way ANOVA). The incidence of ascites development was analyzed by

Chi square (X^2) test, $^{\#}P<0.0001$. Ascites volume in treated mice compared to controls was analyzed by One way ANOVA and unpaired Student's t-test.

Detailed Description

The present disclosure provides a method for treating metastatic cancers comprising intraperitoneal or intravesicle administeration a nanoparticulate formulation of paclitaxel comprising paclitazel encapsulated in a micelle with a diblock copolymer. More specifically, the present disclosure provides a method for intraperitoneal or intravesicle administration a nanoparticulate formulation of paclitaxel comprising infusing a nanoparticulate formulation intraperitoneally at a dose of from about 15 mg/kg/day to about 60 mg/kg/day. More preferably, the intraperitoneal dose of paclitaxel is from 25 mg/kg/day to 50 mg/kg/day. Most preferably, the intraperitoneal dose of paclitaxel is from 30 mg/kg/day to 50 mg/kg/day. Preferably, the nanoparticulate formulation of paclitaxel has a particle size average of 15 nm to 40 nm.

The present disclosure provides paclitaxel-containing pharmaceutical compositions in a micelle, that is stable in protein-free medium and less stable in a protein containing medium. The paclitaxel formulation includes amphiphilic block copolymer which may comprise a hydrophilic block (A) and a hydrophobic block (B) linked with each other in the form of A-B, A-B-A or B-A-B structure. Additionally, the amphiphilic block copolymer forma a core-shell type polymeric micelles in its aqueous solution state, wherein the hydrophobic block forms the core and the hydrophilic block forms the shell. Preferably, the hydrophilic block (A) of the amphiphilic block copolymer is polyethylene glycol (PEG) or monomethoxypolyethylene glycol (mPEG). The hydrophilic block (A) may have a weight average molecular weight of 500-20,000 daltons, specifically 1,000-5,000 daltons, and more specifically 1,000-2,500 daltons. The hydrophobic block (B) of the amphiphilic block copolymer is a water-insoluble, biodegradable polymer. Preferably, the hydrophobic block (B) is polylactic acid (PLA) or poly(lactic-co-glycolic acid) (PLGA). The hydrophobic block (B) has a weight average molecular weight of 500-20,000 daltons, specifically 1,000-5,000 daltons, and more specifically 1,000-2,500 daltons. Hydroxyl end groups of the hydrophobic block (B) are protected with fatty acid groups, such as acetate, propionate, butyrate, stearate, palmitate groups, and the like. The amphiphilic block copolymer comprising the hydrophilic block (A) and the hydrophobic block (B) are present in the pharmacrutical composition in an amount of 20-98 wt %, specifically 65-98 wt %, and more specifically 80-98 wt % based on the total dry weight of the composition.

Alternatively, the hydrophilic block (A) and the hydrophobic block (B) are present in the amphiphilic block copolymer in such a ratio that the copolymer comprises 40-70 wt %, specifically 50-60 wt % of the hydrophilic block (A) based on the weight of the copolymer. When the hydrophilic block (A) is present in a proportion less than 40%, the polymer has undesirably low solubility to water, resulting in difficulty in forming micelles. On the other hand, when the hydrophilic block (A) is present in a proportion greater than 70%, the polymer becomes too hydrophilic to form stable polymeric micelles, and thus the composition may not be used as a composition for solubilizing paclitaxel.

A preferred paclitaxel formulation is IG-001 (also referred to as Genexol-PM) which is a polymeric micelle formulation of paclitaxel. IG-001 has a di-block copolymer composed of methoxy poly (ethylene glycol)-poly (lactide) to form nanoparticles with paclitaxel containing hydrophobic core and a hydrophilic shell. The nanoparticles formed are around 25 nm in diameter, as contrasted with nab-paclitaxel (Abraxane) which has much larger particles of around 120 nm in diameter.

The micellular formulations are quite stable in protein-free media. Sustained release micelles have been prepared in which polymers with very low CMC (< 0.1 μg/ml) can be used for prolonging the circulation time before the micelle degrades. Upon intravenous injection, the micelles undergo dilution in the body. If the CMC of the micelles is high, the concentration of the polymer or surfactant falls below the CMC upon dilution and hence, the micelles dissociate. Therefore, a higher concentration of the polymer or surfactant has to be used to prepare the micelles so that they withstand the dilution up to 5 l in the blood. However, the use of high concentrations might not be feasible due to toxicity related dose limitations. If the polymer or surfactant has a CMC lower than 0.1 μg/ml, concentrations as low as 5 mg/ml may be used to prepare a micelle formulation in order to counter the dilution effects in the blood. A variety of polymers including diblock copolymers, triblock copolymers and graft copolymers have been synthesized to be stable even after intravenous administration.

The smaller nanoparticles, such as IG-001, are more stable in protein-free solutions than in solutions containing proteins such as serum. The nanoparticles may be at least 20% more stable or 25% more stable or 30% more stable or 35% more stable or 40% more stable or 45% more stable or 50% more stable or 55% more stable or 60% more stable or 65% more stable or 70% more stable or 75% more stable or 80% more stable or 85% more stable or 90% more stable or 95% more stable or 100% more stable or 125% more stable or 150% more stable or 175% more stable or 200% more stable or 500% more stable or 1000% more

stable or 5000% more stable or 10000% more stable in a protein free solution than in a solution containing protein. The nanoparticles of the present invention may be between about 10% more stable to about 25000% more stable or about 10% more stable to about 15000% more stable or about 10% more stable to about 12500% more stable or about 10% more stable to about 10000% more stable or from about 10% more stable to about 9000% more stable or from about 10% more stable to about 8000% more stable or from about 10% more stable to about 7000% more stable or from about 10% more stable to about 6000% more stable or from about 1000% more stable to about 500% more stable or from about 10% more stable to about 400% more stable or from about 10% more stable to about 300% more stable or about 10% more stable to about 200% more stable or about 20% more stable to about 125% more stable or about 20% more stable to about 100% more stable or from about 20% more stable to about 90% more stable or from about 20% more stable to about 80% more stable or from about 20% more stable to about 70% more stable or from about 20% more stable to about 60% more stable or from about 20% more stable to about 50% more stable or from about 20% more stable to about 40% more stable or from about 50% more stable to about 2500% or from about 50% more stable to about 1250% more stable or from about 50% more stable to about 1000% more stable in a protein free solution than in a solution containing protein.

Nanoparticles are less stable in solutions or media containing proteins such as serum than nab-paclitaxel. The nanoparticles of the present invention may be at least 20% less stable or 25% less stable or 30% less stable or 35% less stable or 40% less stable or 45% less stable or 50% less stable or 55% less stable or 60% less stable or 65% less stable or 70% less stable or 75% less stable or 80% less stable or 85% less stable or 90% less stable or 95% less stable or 100% less stable or 125% less stable or 150% less stable or 175% less stable or 200% less stable or 500% less stable or 1000% less stable or 5000% less stable or 10000% less stable in a protein free solution than in a solution containing protein. The nanoparticles of the present invention may be between about 10% less stable to about 25000% less stable or about 10% less stable to about 15000% less stable or about 10% less stable to about 12500% less stable or about 10% less stable to about 10000% less stable or from about 10% less stable to about 9000% less stable or from about 10% less stable to about 8000% less stable or from about 10% less stable to about 7000% less stable or from about 10% less stable to about 6000% less stable or from about 1000% less stable to about 500% less stable or from about 10% less stable to about 400% less stable or from about 10% less stable to about 300% more stable or about 10% more stable to about 200% more stable or about 20% more stable to

about 125% more stable or about 20% more stable to about 100% more stable or from about 20% more stable to about 90% more stable or from about 20% more stable to about 80% more stable or from about 20% more stable to about 70% more stable or from about 20% more stable to about 60% more stable or from about 20% more stable to about 50% more stable or from about 20% more stable to about 40% less stable or from about 50% less stable to about 2500% or from about 50% less stable to about 1250% less stable or from about 50% less stable to about 1000% less stable in a protein free solution than in a solution containing protein.

The compositions show similar or the same pharmacokinetics in mice and humans as nab-paclitaxel.

Table 1 (in mice)

Drug	Half Life (hr)	T_{max} (hr)	AUC_{inf} (hr*ng/ml)	Vz (ml/kg)	CI (ml/hr/kg)
Abraxane	2.99	0.08	61561.33	2103.71	487.32
IG-001	2.83	0.08	58151.31	2103.58	515.90

Table 2 shows a comparison of mean non-compartmental pharmacokinetic parameters of nab-paclitaxel and IG-001 of a 3 hour infusion, 135 mg/m^2 dose.

Table 2 (in humans)

Drug	C_{max} (ng/ml)	AUC_{inf} (hr*ng/ml)	Half Life (hr)	CI (l/hr/m^2)
IG-001	1357	5473	12.7	25.5
Nab-paclitaxel	1392	5654	12.9	27.4

IG-001 and nab-paclitaxel also show similar or the same clinical efficacy as measured by overall response rate in Phase III clinical trials for metastatic breast cancer (See Figure 7).

IG-001 exhibited significant instability in serum even at high paclitaxel concentrations of 2000 µg/ml. Conversely, nab-paclitaxel ceased to exist as a nanoparticle starting at 200 µg/ml paclitaxel concentrations. IG-001 had expanded PK proportionality and higher MTD as compared to nab-paclitaxel (See Figures 3 and 4). Moreover, IG-001 exhibits a remarkable stability in protein-free matrices even at low paclitaxel concentrations of 4 µg/ml. Conversely, nab-paclitaxel ceased to exist as a nanoparticle starting at 40 µg/ml paclitaxel concentrations. IG-001 is suitable for intraperitoneal and/or intravesicle modes of drug delivery due to higher nanoparticle residence time and the reduced likelihood of paclitaxel precipitation.

Example 1

A comparison of dissolution/instability profiles of nab-paclitaxel and IG-001 was conducted in serum-containing (1X FBS, 0.1 X FBS) and protein-free (1X PBS) matrices at

37^{0}C using Dynamic Light Scattering (DLS) methodology (Malvern's Zetasizer Nano S and Wyatt's Nanostar). The results of the study are displayed in Figures 1 and 2. IG-001 had a 10-fold diminished stability versus Abraxane in serum. IG-001 exhibited significant instability in serum even at high paclitaxel concentrations of 2000 ug/ml. Conversely, Abraxane ceased to exist as a nanoparticle starting at about 200 ug/ml paclitaxel concentrations. This data may explain the observed expanded PK proportionality and the higher maximum tolerated does (MTD) of IG-001 vs. Abraxane.

IG-001 has 10-fold enhanced stability compared to Abraxane in protein-free matrices. IG-001 exhibited remarkable stability (high CMC) in protein-free matrices even at low paclitaxel concentrations of 4 ug/ml. Conversely, Abraxane ceased to exist as a nanoparticle starting at 40 μg/ml paclitaxel concentrations. Significance of these findings is the better suitability of IG-001 for intraperitoneal and/or intravesicle modes of drug delivery due to higher nanoparticle residence time and the reduced likelihood of paclitaxel precipitation. IG-001 exhibits exceptional stability in protein-free fluid- suitable for intraperitoneal administration for ovarian cancer and intravesicle administration for bladder cancer. IG-001 is highly unstable in serum and therefore shows expanded PK-proportionality making a higher MTD possible.

Example 2

Phase 1 study of IG-001with Carboplatin as a Primary Treatment in Patients with Advanced Ovarian Carcinoma

A Phase 1 study of IG-001, a novel Cremophor-free, polymeric micelle formulation of paclitaxel with carboplatin as a primary treatment in patients with advanced ovarian carcinoma was conducted to determine the Maximum Tolerated Dose (MTD) and dosing for Phase 2 trial of IG-001 in combination with carboplatin. Other objectives included overall survival, progress free survival, time to progression, duration of overall response and safety and toxicity. Six patients/dose level were treated with 220, 260, and 300 mg/ in a manner shown in Table 1. MTD was not determined in this phase 1 trial (over 300mg/m^2)

Table 3

Group	Total cycles	Investigator Evaluation	Best Overall Response (Reviewer Evaluation)
220mg/m²	6 cycle	PR	PR
	6 cycle	CR	PR
	6 cycle	PR	PR
	2 cycle	PR	PR
	6 cycle	CR	PR
	6 cycle	PR	PR
260mg/m²	6 cycle	PR	PR
	6 cycle	PR	PR
	6 cycle	PR	PR
	2 cycle	PD	PD
	6 cycle	CR	PR
	6 cycle	CR	CR
300mg/m²	1 cycle	NA	PR
	6 cycle	PR	PR
	2 cycle	PR	PR
	6 cycle	CR	CR
	6 cycle	CR	PR
	6 cycle	PR	PR

Dose Limiting Toxicity was shown as grade 4 myalgia in one patient at 300 mg/m^2. The result indicated a response rate of 94.12%, adverse events: 20.64% and LT toxicity: 7.83%. No death related to the disease or treatment. The recommended dose for Phase 2 trial of cremophor-free paclitaxel in combination with Carboplatin was 260mg/m^2.

Example 3

Combination Therapy of IG-001 Plus Carboplatin Compared to Paclitaxel Plus Carboplatin as a 1st line Treatment in Patients with Epithelial Ovarian Cancer

Ovarian trial design: randomized, two-arm trial, primary advanced epithelial ovarian cancer consisting of 100 patients (50/each arm). Control Arm: Solvent based paclitaxel 175mg/m2 IV + Carboplatin 5 AUC IV, 3 weeks, 6 cycles and Experimental Arm: IG-001 260mg/m^2 IV + Carboplatin 5 AUC IV 3 weeks, 6 cycles.

Table 4

	Response n (%)	C.I.	Patients n(%)	p-value
Experiment (IG-001 + Carboplatin	44 (88.00	(80.44, 95.56)	50 (51.02)	0.7005
Control (Paclitaxel + Carboplatin)	37 (77.08)	(67.10, 87.06)	48 (48.98)	
Total	81 (82.65	(76.36, 88.95)	98 (100.00)	
Experimental group – control group	-10.92	(-∞,1.60)		

Table 5

		Rate (%)	Number (n)	Pt. No. n(%)	p-value
AE	IG-001 + Carboplatin	50 (100.00)	418	50 (51.02)	0.0539
	Paclitaxel + Carboplatin	44 (91.67)	360	48 (48.98)	
	Total	94 (95.92)	778	98 (100.00)	
SAE	IG-001 + Carboplatin	20 (40.00)	51	50 (51.02)	0.3662
	Paclitaxel + Carboplatin	15 (31.25)	37	48 (48.98)	
	Total	35 (35.71)	88	98 (100.00)	
UAE	IG-001 + Carboplatin	1 (2.00)	1	50 (51.02)	1.0000
	Paclitaxel + Carboplatin	0 (0.00)	0	48 (48.98)	
	Total	1 (1.02)	1	98 100.00)	

The results indicate that the response rate was 88.00% vs. 77.8% (IG-001 vs. paclitaxel) and the primary endpoint of noninferiority to paclitaxel was met. The one-sided 95% upper confidence limit was 4.95, which is lower than the non-inferiority threshold (16.3%), indicating that the study group is not inferior to the control group. Adverse events were similar to paclitaxel despite the higher dose.

Example 4

A total of 186 subjects were enrolled and had surveillance data sheets collected and efficacy and safety assessments were conducted. The initial dose of IG-001 was 300 mg/m^2 with possible dose reductions in 2 stages based on hematological and non-hematological toxicities (except for alopecia) to 240 mg/m^2 and 190 mg/m^2. The mean age of the subjects was 50.31 years with a range of 29 to 75 years. The disease duration ranged from 0.33 to 312 months with a mean duration of 64.44 months. There were 180 subjects (96.77%) with stage IV disease and 6 subjects (3.23%) with stage III disease. There were 81 subjects (97.31%) with prior treatment for breast cancer including 174 subjects (96.13%) with prior chemotherapy.

The results of the efficacy study indicated that 36 of the 148 evaluable subjects (24.32%) responded to the drug treatment and were judged to be efficacious.

Table 6

	Number of Subjects	Percent (%)
CR (complete response)	0	0.00
PR (partial response)	36	24.32
SD (stable disease)	53	35.81
PD (progressive disease)	58	39.19

Unevaluable	1	0.68

One factor which correlated with efficacy was the total number of drug treatment cycles ($p < 0.0001$)

Table 7

Cycles	Efficacious (N) (%)	95% CI (upper and lower limit	Inefficacious (N) (%)	Total (N) (%)	p-value
1	0 (0.00)	(0.00, 0.00)	3 (100.00)	3 (2.03)	
2	0 (0.00)	(0.00, 0.00)	13 (100.00)	13 (8.78)	
3	0 (0.00)	(0.00, 0.00)	37 (100.00)	37 (25.00)	
4	2 (14.29)	(0.00, 32.62)	12 (85.71)	14 (9.46)	
5	3 (37.50)	(3.95, 71.05)	5 (62.50)	8 (5.41)	
6	19 (39.58)	(25.75, 53.42)	29 (60.42)	48 (32.43)	
7	2 (100.00)	(100.00, 100.00)	0 (0.00)	2 (1.35)	
8	0 (0.00)	(0.00, 0.00)	5 (100.00)	5 (3.38)	
9	7 (58.33)	(30.44, 86.23)	5 (41.67)	12 (8.11)	
Over 9	3 (50.00)	(9.99, 90.01)	3 (50.00)	6 (4.05)	
Totals	36 (24.32)	(17.41, 31.24)	112 (75.68)	148 (100.00)	

145 subjects (77.96%) reported at least one TEAE on study and there were a total of 710 adverse events. The most frequent TEAEs were neutropenia (23.12%), peripheral neuropathy (18.82%), nausea (16.13%), myalgia (13.98%), leukopenia (13.44%), peripheral sensory neuropathy (11.29%), tingling (10.22%), decreased hemoglobin (9.68%), alopecia (9.14%), loss of appetite (9.14%), neuropathy (8.60%), pruritus (5.91%), vomiting (5.91%), general weakness (5.38%), dyspnea (5.38%) headache (5.38%), rash (4.84%) and cough (4.84%). Urticaria was reported in 1 subjects (0.54%). Hypotension occurred in 3 subjects (1.61%). Thrombocytopenia occurred in 6 subjects (3.23%). Of the 710 TEAEs, 307 (43.24%) were Grade 1 in severity, 252 (35.49%) were Grade 2, 94 (13.24%) were Grade 3, 55 (7.75%) were Grade 4 and 2 (0.28%) were Grade 5. 620 TEAEs (87.32%) were related or unknown and 90 (12.68%) were not related to study drug.

Example 5

This example provides the results of a study designed to compare the *in vivo* efficacy of two formulations of nanoparticle-encapsulated paclitaxel: IG-001 and Abraxane (nab-paclitaxel) in a preclinical mouse model of human ovarian cancer peritoneal metastasis. IG-001 was delivered intraperitoneally and Abraxane was delivered intravenously. One established ovarian cancer cell line (IGROV-1; Developmental therapeutic program, NCI, Frederick, MD) were used for tumor implantation studies. Five to six-weeks old athymic female nu^+/nu^+ mice (Harlan) were used. All studies were done in compliance with the University of Virginia ACUC regulation under the approved protocol# 3879 (PI. Said). Mice

were housed in specific pathogen-free environment with 12 hours light/dark cycles at the University of Virginia vivarium. Mice were injected intra-peritoneally (ip) with $2x10^6$ cells/100µl Dulbecco's phosphate buffered saline (DPBS). Mice were assigned into experimental groups initiated 7 days post tumor inoculation with the day of injection assigned ad Day 0:

Group A: Control, injected with 50µl saline; n=12

Group B: Abraxane (ABX) 15 mg/kg/d, qdx5; n=10---Administered intravenously (i.v.)

Group C: Abraxane (ABX) 30 mg/kg/d, qdx5; n=10---Administered i.v.

Group D: IG-001 (Pax) 15 mg/kg/d, qdx5; n=10---Administered i.p.

Group E: IG-001 (Pax) 30 mg/kg/d, qdx5; n=10---Administered i.p.

Group F: IG-001 (Pax) 60 mg/kg/d, qdx5; n=11---Administered i.p.

Group G: IG-001 (Pax) 90 mg/kg/d, qdx5; n=13---Administered i.p.

Mice were monitored twice/week for 12 weeks as follows:

1. % weight loss/gain: weekly weight measurement, % weight change from day 0 (weight at the time of injection of tumor cells *vs.* post-treatment).
2. Survival Time (Kaplan-Meier, K-M plot).
3. Presence/extent of intra-peritoneal tumor growth and the development of ascites.

One week after tumor cell injection, mice were assigned into the aforementioned cohorts**.** Examining the changes of the mice weights revealed that all mice receiving IG-001 (Pax) and Abraxane (ABX) experienced weight loss after initiation of treatment (~15-17% from the control untreated mice, (Figure 8) with no significant difference between the mice receiving comparable doses of both drugs. Mice steadily gained weight after cessation of treatment. Experimental cohorts treated with higher doses of IG-001 90 m/kg/d dose exhibited profound weight loss, lethargy and triggering humane euthanasia at 3 days (8/13) and 5 days (5/13) after initiation of treatment (Table 8). Four mice (4/11) treated with 60 m/kg/d IG-001 also exhibited the same signs after 5 doses and did not survive the study. The latter were excluded from the study analyses *vide infra.*

Table 8

	Died after 3 doses	Died after 5 doses	Continued study/total
control	0	0	12/12
Mice treated with treated 15 mg/kg/d qdX5	0	0	10/10
Mice treated with treated 30 mg/kg/d qdX5	0	0	10/10
Mice treated with treated 60 mg/kg/d qdX5	0	4	7/11*

Mice treated with treated 90 mg/kg/d qdX5	8	5	0/13*

(* $p<0.0001$ X^2 test)

Effect of Treatment on the survival of experimental groups: Treatment with either ip IG-001 or iv ABX (nab-paclitaxel) significantly increased the median survival of mice compared to untreated control (Figure 9). Intraperitoneal treatment with IG-001 conferred significant increase in median survival compared to similar doses of iv ABX (Figure 9).

Analysis of Kaplan Meier survival curves (Mantel-Cox analysis) of IG-001 treated cohorts indicated significant dose-dependent survival advantage (Figure 10). ABX-treated cohorts did not exhibit dose-dependent survival advantage (Figure 10). Intraperitoneal IG-001 treatment significantly conferred survival advantage over iv ABX at 15 and 30 mg/kg/d.

Evaluation of Intra-abdominal Tumor Burden: Because mice weights did not represent the actual intraperitoneal tumor burden, we developed an arbitrary score for tumor burden to account for the intra-peritoneal spread to various organs as liver, diaphragm, omentum, mysentry as well as the ascitic fluid volume measured at the time of euthanasia. This score accounts for tumor size and multiplicity in a given organ. The total score of each animal is calculated and the mean values/cohort were analyzed.

In vivo response of IGROV1 tumor xenografts to IG-001 intraperitoneal treatment: Intraperitoneal injection of Pax significantly decreased IGROV1 intraperitoneal tumor burden (Figure 11) in a dose-dependent manner. The incidence of ascites development in mice treatment with ip IG-001 was significantly decreased after treatment with 15 mg/kg/d and 30 mg/kg/d (Figure 11). Ascites volume significantly decreased in mice treated with 15 mg/kg/d and 30 mg/kg/d compared to control untreated group. Mice treated with 60 mg/kg/d did not develop ascites. No significant difference was observed between cohorts treated with 15 and 30 mg/kg/d.

In vivo response of IGROV1 tumor xenografts to Abraxane intravenous treatment: Intravenous Abraxane treatment significantly decreased intra-peritoneal tumor burden in a dose-dependent manner (Figure 12). The incidence of ascites development in mice treatment with iv ABX significantly decreased only after treatment with 30mg/kg/d (Figure 12). Ascites volume significantly decreased in mice treated with 15 mg/kg/d and 30 mg/kg/d compared to controls. A significant difference was observed between ascites volumes from cohorts treated with 15 mg/kg/d and 30 mg/kg/d (Figure 12).

At the time of euthanasia, tumor burden in mice treated with IG-001 (ip) was significantly less than those treated with the same doses of iv ABX (Figure 13). Consistently,

ascitic fluid volume in mice treated with 15 mg/kg/d ip IG-001 was significantly less than that in mice treated with the same dose of iv ABX (Figure 13). However, no significant difference was observed in ascitic fluid volume in mice treated with 30 mg/kg/d of either drug.

Accordingly, Example 5 shows:

1. Intraperitoneal IG-001 was well tolerated at doses of 15-60 mg/kg/d but not at 90 mg/kg/d.

2. Tumor-bearing mice treated with intraperitoneal IG-001 exhibited significantly longer median survival than counterparts treated with the same doses of intravenous Abraxane.

3. Intraperitoneal tumor burden and the development of ascites (incidence and volume) were significantly decreased in mice treated with intraperitoneal IG-001 compared to mice treated with similar doses of intravenous Abraxane.

4. A therapeutic dose of 60 mg/kg/d of intraperitoneal IG-001 was associated with better clinical outcome than 15 and 30 mg/kg/d; however, it was associated with morbidity and mortality in (4/11 mice, 36.4%) after initiation of treatment.

We claim:

1. A method for treating peritoneal metastatic cancers comprising administering a nanoparticulate formulation of paclitaxel intraperitoneally.

2. A method for treating metastatic cancers comprising intraperitoneal or intravesicle administration a nanoparticulate formulation of paclitaxel comprising paclitaxel encapsulated in a micelle with a diblock copolymer.

3. The method for treating metastatic cancers of claim 2, wherein the paclitaxel dose of from about 15 mg/kg/day to about 60 mg/kg/day.

4. The method for treating metastatic cancers of claim 3, wherein the paclitaxel dose is from 25 mg/kg/day to 50 mg/kg/day.

5. The method for treating metastatic cancers of claim 3, wherein the paclitaxel dose is from 30 mg/kg/day to 50 mg/kg/day.

6. The method for treating metastatic cancers of claim 2, wherein the nanoparticulate formulation of paclitaxel has a particle size average of 15 nm to 40 nm.

7. The method for treating metastatic cancers of claim 2, wherein the amount of paclitaxel administered is at least 190 mg/m^2.

Figure 1

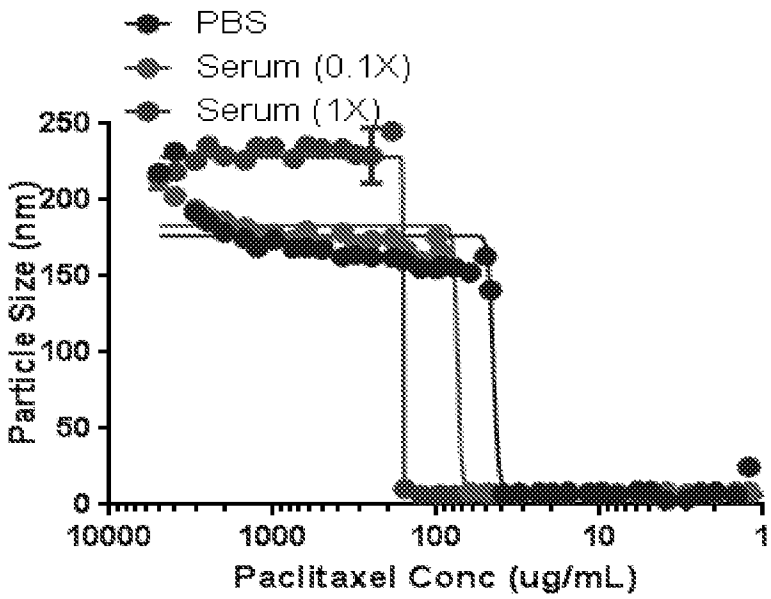

PBS
Serum (0.1X)
Serum (1X)
Particle Size (nm)
250
200
150
100
50
0
10000
1000
100
10
1
Paclitaxel Conc (ug/mL)

Figure 2

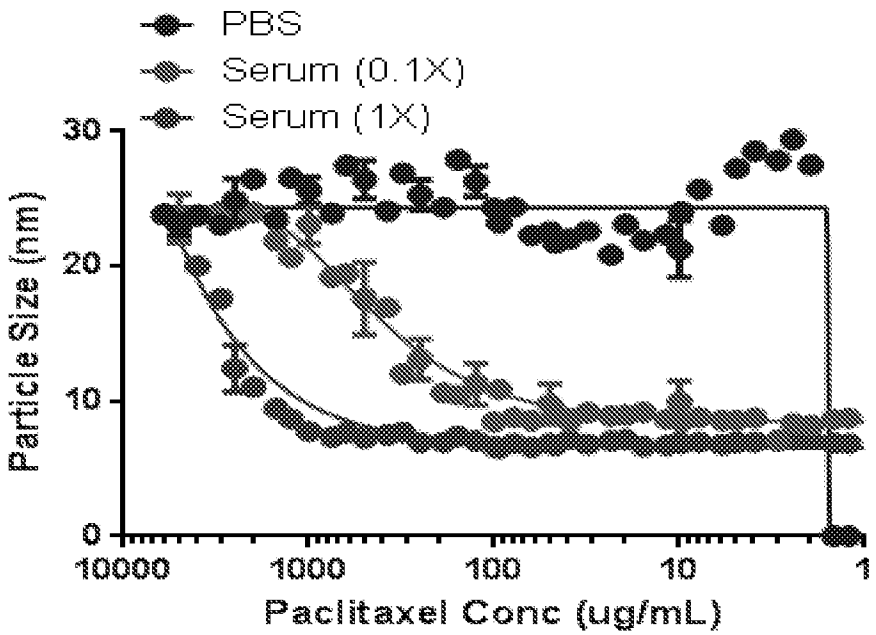

PBS
Serum (0.1X)
Serum (1X)
Particle Size (nm)
30
20
10
0
10000
1000
100
10
1
Paclitaxel Conc (ug/mL)

Figure 3

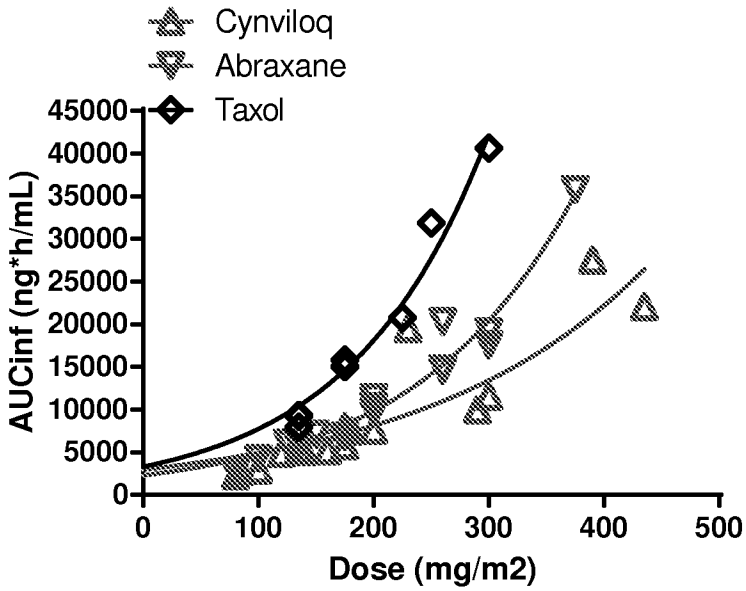

Cynviloq
Abraxane
Taxol
AUCinf (ng*h/mL)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0
100
200
300
400
500
Dose (mg/m2)

Figure 4

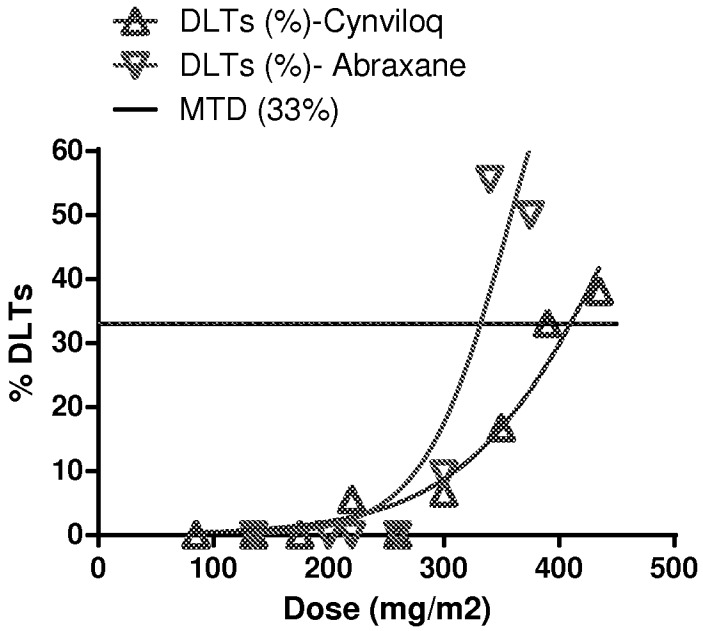

DLTs (%)-Cynviloq
DLTs (%)- Abraxane
MTD (33%)
% DLTs
60
50
40
30
20
10
0
0
100
200
300
400
500
Dose (mg/m2)

Figure 5

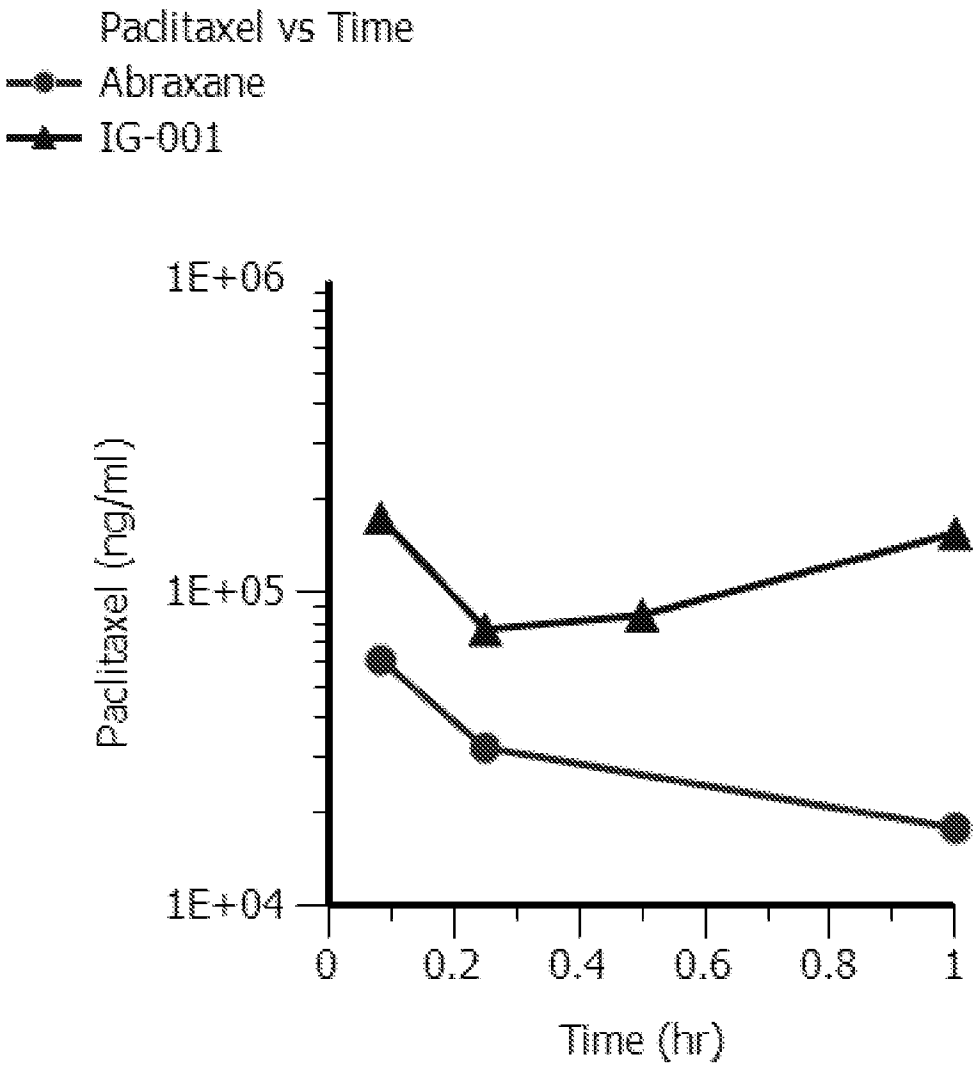
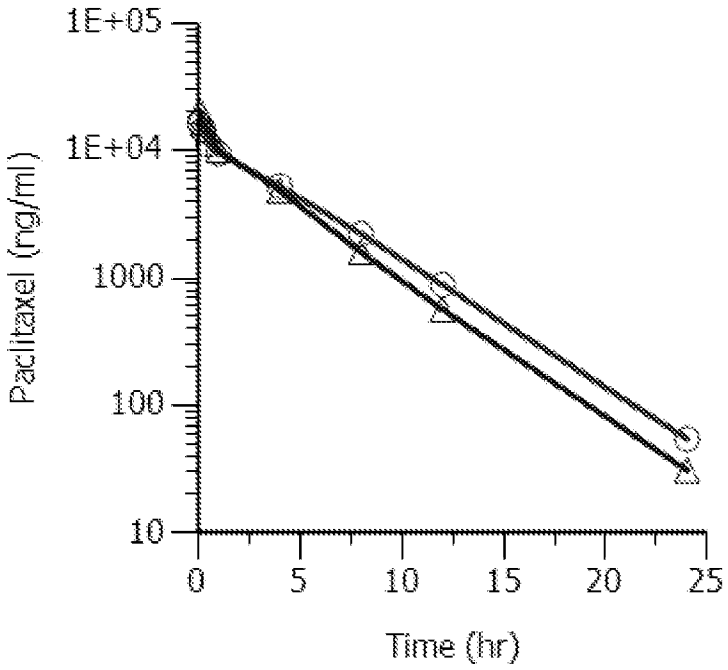

Paditaxel vs Time
Abraxane
IG-001
1E+06
1E+05
1E+04
Paclitaxel (ng/ml)
0
0.2
0.4
0.6
0.8
1
Time (hr)

Figure 6A


1E+05
1E+04
1000
100
10
Paclitaxel (ng/ml)
0
5
10
15
20
25
Time (hr)

B

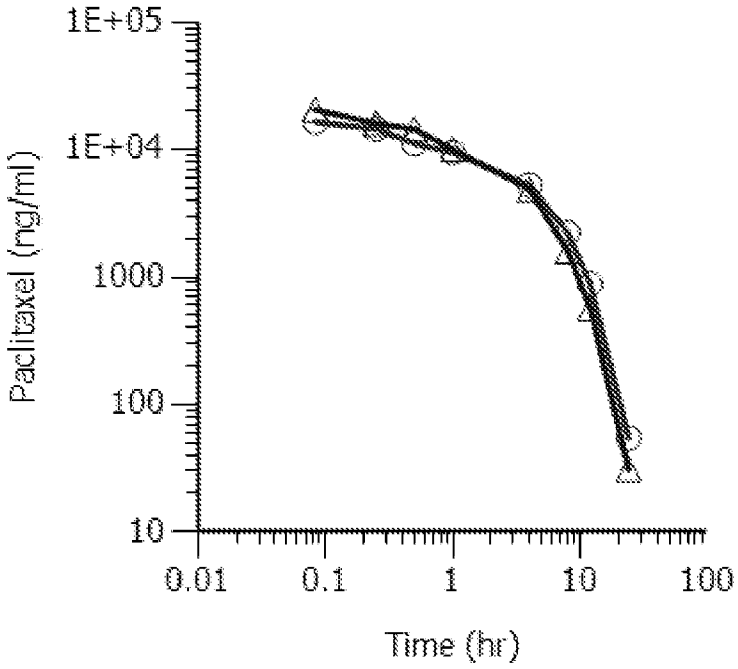

1E+05
1E+04
1000
100
10
Paclitaxel (ng/ml)
0.01
0.1
1
10
100
Time (hr)

Figure 7

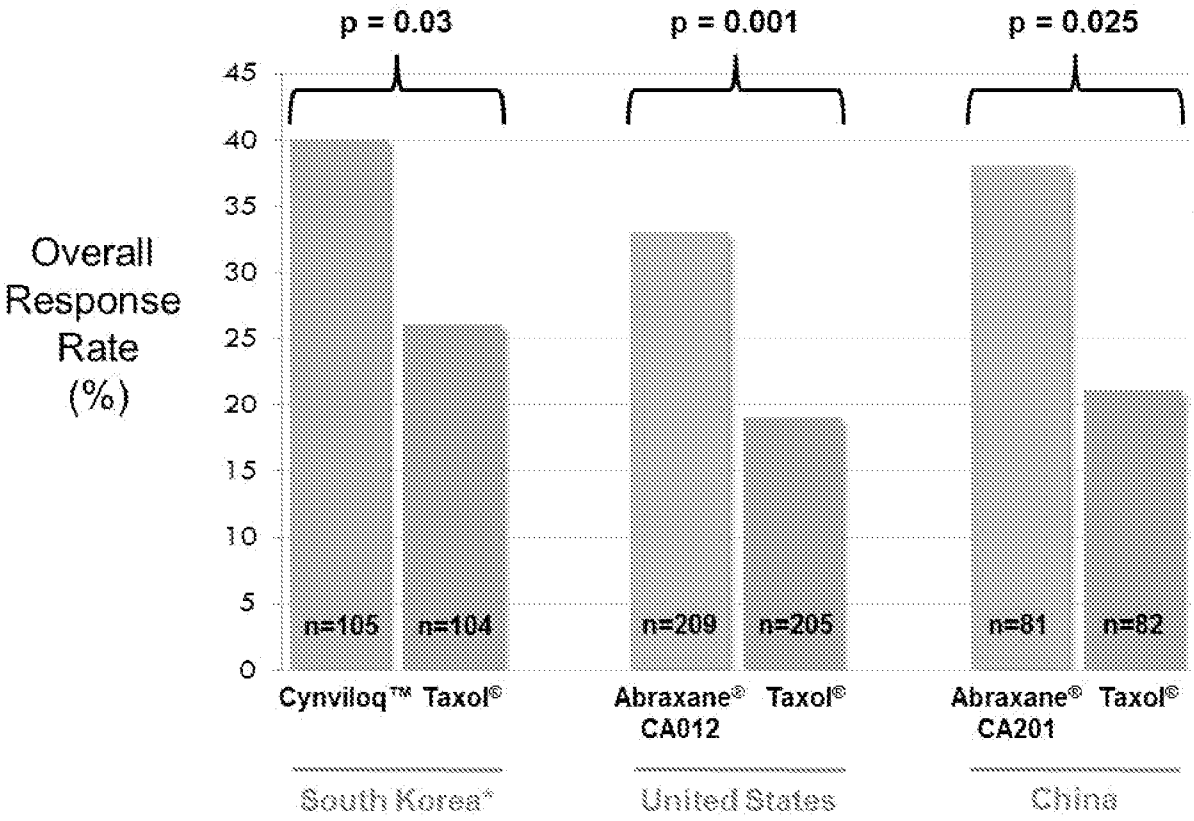


Figure 8

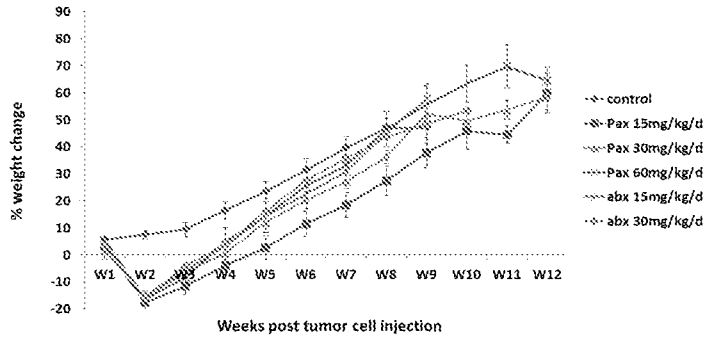
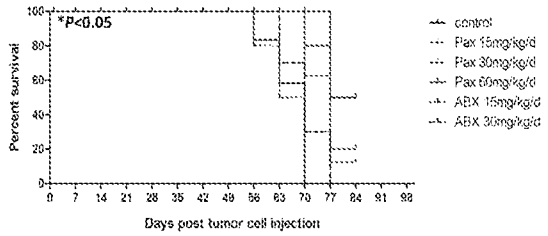


Figure 9



	control	Pax 15mg/kg/d	Pax 30mg/kg/d	Pax 60mg/kg/d	ABX 15mg/kg/d	ABX 30mg/kg/d
Median Survival (days)	63	77*^	77*	80.5*	66.5*^	70*

Figure 10

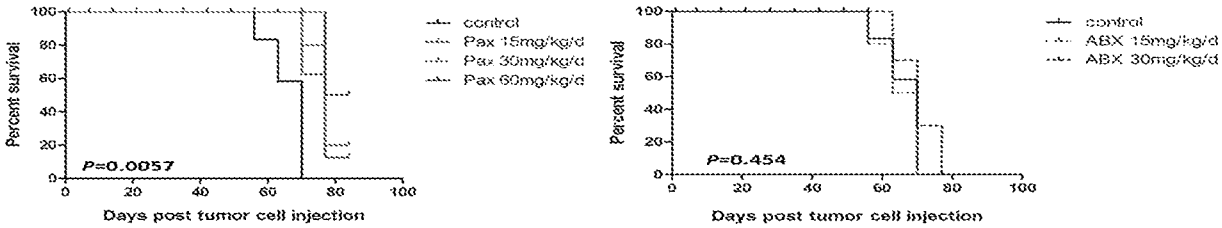


Figure 11

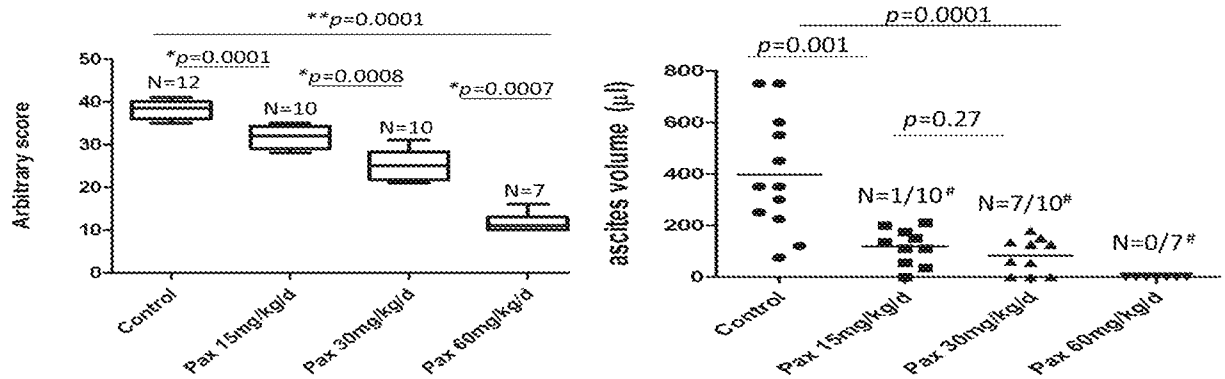


Figure 12

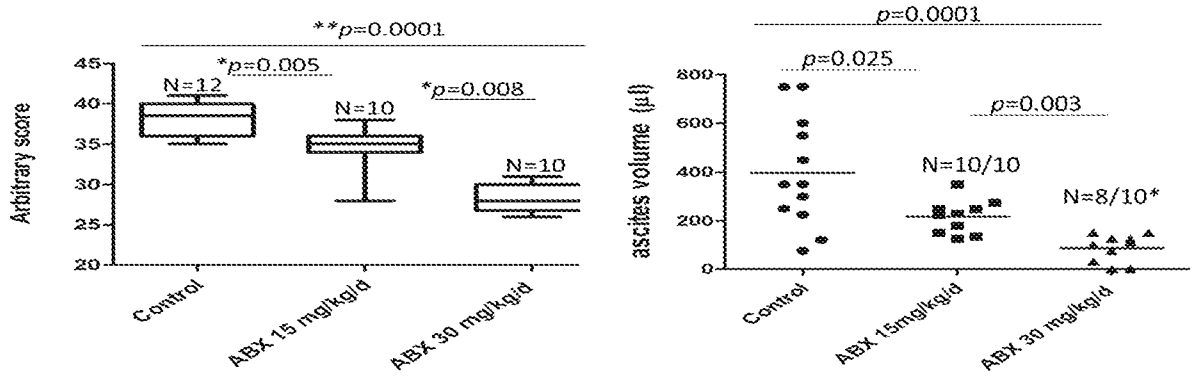
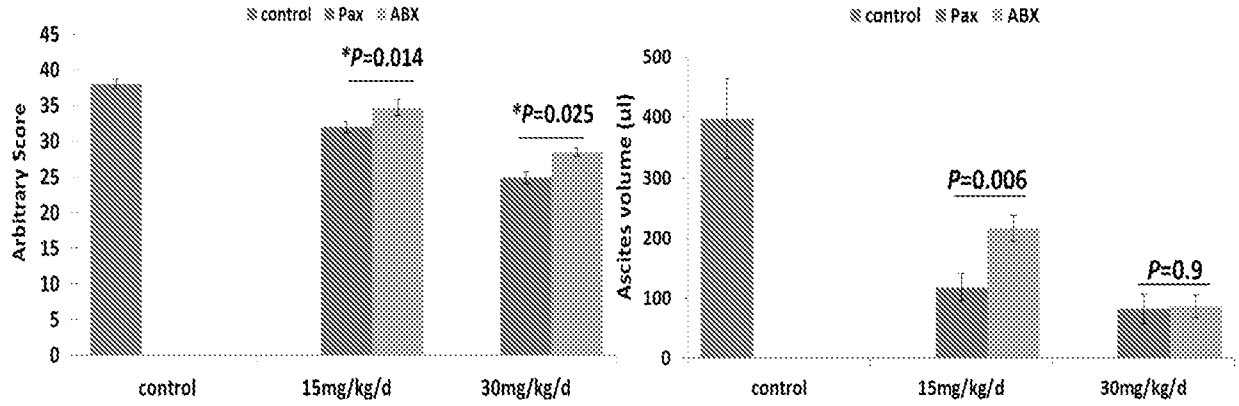


Figure 13



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/59207

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/07, 9/51, 31/337 (2014.01)
CPC - A61K 31/337, 9/0019, 9/1075
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) Classification(s): A61K 9/07, 9/51, 31/337 (2014.01)
CPC Classification(s): A61K 31/337, 9/0019, 9/1075; USPC Classification(s): 424/400, 490; 514/449

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; Google/Google Scholar; IP.com; KEYWORDS: nano*partic*, nano*met*, nano*cryst*, nm, paclitaxel*, Taxol*, Onxol*, Paxene*, Praxel*, intra*peritoneal*, cancer*, carcin*, *oma, di*block, co*polymer*, micelle*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	XIAO, K et al. "A self-assembling nanoparticle for paclitaxel delivery in ovarian cancer" Biomaterials 2009, Volume 30; pages 6006-6016; abstract; page 6008, sections 2.8-2.9 ; page 6013, section 3.6	1 -- 4-5
X -- Y	US 8,383,136 B2 (KWON, GS) 26 February 2013; column 3, lines 34-61; column 10, lines 1-17; column 20, line 62 to column 21, line 11; column 25, lines 37-56; column 39, lines 20-33; claims 1, 12	2-3, 6-7 -- 4-5
X	WO 2005/040247 A1 (SAMYANG CORPORATION) 06 May 2005; page 11, lines 6-17; page 19, lines 3-20; page 21, lines 10-13; page 59, lines 23-27	2-5
A	US 8,043,631 B2 (AU, JLS et al.) 25 October 2011; entire document	1-7
A	US 2003/0157161 A1 (HUNTER, WL et al.) 21 August 2003; entire document	1-7
A	US 2008/0160095 A1 (Desai, NP et al.) 03 July 2008; entire document	1-7
A	US 2010/0069426 A1 (ZALE, SE et al.) 18 March 2010; entire document	1-7
A	US 2011/0158906 A1 (MULLEN, K et al.) 30 June 2011; entire document	1-7
A	US 2012/0231053 A1 (AKATSU, Y et al.) 13 September 2012; entire document	1-7
A	WO 2001/021174 A1 (DABUR RESEARCH FOUNDATION) 29 March 2001; entire document	1-7
A	WO 2012/070029 A1 (CHIRWA, N et al.) 31 May 2012; entire document	1-7

☒ Further documents are listed in the continuation of Box C. ☐

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

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2014 (26.11.2014)	02 JAN 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/59207

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/158960 A2 (GILLIES, RJ et al.) 22 November 2012; entire document	1-7