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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 November 2012 (22.11.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/158776 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2012/038111

(22) International Filing Date:
16 May 2012 (16.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/487,232 17 May 2011 (17.05.2011) US

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF SOUTH ALABAMA** [US/US]; 775 University Boulevard, Building II, Suite 150, Mobile, AL 36608 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **KHONG, Hung** [US/US]; c/o : University Of South Alabama, 775 University Boulevard, Building II, Suite 150, Mobile, AL 36608 (US).

(74) Agent: **HART, Daniel**; Knobbe Martens Olson & Bear LLP, 2040 Main Street, Fourteenth Floor, Irvine, CA 92614 (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, 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, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, 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, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *of inventorship (Rule 4.17(iv))*

**Published**:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/158776 A2

(54) **Title**: COMBINATION THERAPY FOR TREATMENT OF CANCER

(57) **Abstract**: The present invention relates to methods and compositions for the treatment of cancer. Some embodiments include methods of treating cancer comprising administering a chemotherapeutic agent associated with albumin, administering a second chemotherapeutic agent; and administering a third chemotherapeutic agent.

# COMBINATION THERAPY FOR TREATMENT OF CANCER

## RELATED APPLICATIONS

**[0001]** This application claims the benefit of U.S. Provisional Application No. 61/487232 entitled "COMBINATION THERAPY FOR TREATMENT OF CANCER" filed May 17, 2011, the disclosure of which is incorporated herein by reference in its entirety.

## FIELD OF THE INVENTION

**[0002]** The present invention relates to methods and compositions for the treatment of cancer. Some embodiments include methods of treating cancer comprising administering a chemotherapeutic agent associated with or bound to albumin, administering a second chemotherapeutic agent; and administering a third chemotherapeutic agent.

## BACKGROUND OF THE INVENTION

**[0003]** Breast cancer is the most common cancer among women (excluding basal and squamous cell skin cancer) in the U.S. and is the second most common cause of cancer death among women. In the year 2007, the estimated new cases of breast cancer among women in the U.S. is 178,480 and the estimated death from breast cancer is 40,460 (1).

**[0004]** Neoadjuvant chemotherapy for breast cancer is the use of chemotherapy before definitive surgical therapy such as lumpectomy or mastectomy. Compared with adjuvant or postoperative chemotherapy, neoadjuvant chemotherapy allows higher rates of breast conservation without compromising overall survival (2). In addition, neoadjuvant chemotherapy permits a unique opportunity to observe and evaluate tumor response to treatment and therefore, serving as an *in vivo* chemosensitivity assay. This may allow the tailoring of treatment for individual patients based on their tumor response to a particular chemotherapy regimen (3-5). This may potentially enhance response and survival and at the same time reduce unnecessary toxicities.

**[0005]** Not only neoadjuvant chemotherapy does result in similar overall survival compared with adjuvant chemotherapy, it is also associated with less adverse toxicities (6). Compared with adjuvant chemotherapy, neoadjuvant chemotherapy is associated with significantly less infectious complications and cardiotoxicity (6). In addition, there is suggestive evidence that neoadjuvant chemotherapy may be superior to adjuvant chemotherapy on survival

outcome (7). In contrast with adjuvant chemotherapy, there is currently no clear recommendation on neoadjuvant chemotherapy regimens. There is a need for improved therapies for cancer.

## SUMMARY OF THE INVENTION

**[0006]** Some embodiments of the present invention include methods of treating a cancer in a subject in need thereof comprising administering a chemotherapeutic agent associated with or bound to albumin; administering a second chemotherapeutic agent; and administering a third chemotherapeutic agent.

**[0007]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered periodically.

**[0008]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and a third chemotherapeutic agent are administered on the same day and subsequently the chemotherapeutic agent associated with or bound to albumin is administered periodically without the second chemotherapeutic agent and the third chemotherapeutic agent.

**[0009]** In some embodiments, on some occasions the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and a third chemotherapeutic agent are administered on the same day and on other occasions only the chemotherapeutic agent associated with or bound to albumin is administered.

**[0010]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin comprises an agent selected from the group consisting of paclitaxel, docetaxel, and rapamycin.

**[0011]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is Abraxane.

**[0012]** In some embodiments, the second chemotherapeutic agent comprises a topoisomerase inhibitor.

**[0013]** In some embodiments, the topoisomerase inhibitor is doxorubicin.

**[0014]** In some embodiments, the third chemotherapeutic agent comprises an alkylating agent.

**[0015]** In some embodiments, the alkylating agent is cyclophosphamide.

**[0016]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1 and 8.

**[0017]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15.

**[0018]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15, and 22.

**[0019]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15, 22, and 28.

**[0020]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, and 22.

**[0021]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 5 days.

**[0022]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 6 days.

**[0023]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 7 days.

**[0024]** In some embodiments, the periodic administration comprises at least 2 cycles.

**[0025]** In some embodiments, the periodic administration comprises at least 5 cycles.

**[0026]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and the third chemotherapeutic agent are administered on the same day and subsequently the administration of the chemotherapeutic agent associated with or bound to albumin is repeated for a plurality of cycles.

**[0027]** In some embodiments, the plurality of cycles for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least 2 cycles.

**[0028]** In some embodiments, the plurality of cycles for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least 5 cycles.

**[0029]** In some embodiments, each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 5 days.

**[0030]** In some embodiments, each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 6 days.

**[0031]** In some embodiments, each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 7 days.

**[0032]** In some embodiments, each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 1 week.

**[0033]** In some embodiments, at least about 100 mg/m$^2$ Abraxane is administered on day 1 and 8, at least about 50 mg/m$^2$ doxorubicin is administered on day 1, and at least about 500 mg/m$^2$ cyclophosphamide is administered on day 1.

**[0034]** Some embodiments also include administering Pegfilgrastim on day 9.

**[0035]** In some embodiments, the cancer is breast cancer.

**[0036]** In some embodiments, the cancer is HER2 negative breast cancer.

**[0037]** In some embodiments, the cancer is triple negative breast cancer.

**[0038]** In some embodiments, the dose of Abraxane is between about 50 mg/m$^2$ and about 200 mg/m$^2$.

**[0039]** In some embodiments, the dose of Abraxane is selected from the group consisting of 100 mg/m$^2$ and 150 mg/m$^2$.

**[0040]** Some embodiments include use of a combination comprising a chemotherapeutic agent associated with or bound to albumin, a second chemotherapeutic agent, and a third chemotherapeutic agent for the treatment of cancer.

**[0041]** In some embodiments, the the chemotherapeutic agent associated with or bound to albumin is administered periodically.

**[0042]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and a third chemotherapeutic agent are administered on the same day and subsequently the chemotherapeutic agent associated with or bound to albumin is administered periodically without the second chemotherapeutic agent and the third chemotherapeutic agent.

**[0043]** In some embodiments, on some occasions the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and a third chemotherapeutic agent are administered on the same day and on other occasions only the chemotherapeutic agent associated with or bound to albumin is administered.

**[0044]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin comprises an agent selected from the group consisting of paclitaxel, docetaxel, and rapamycin.

**[0045]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is Abraxane.

**[0046]** In some embodiments, the second chemotherapeutic agent comprises a topoisomerase inhibitor.

**[0047]** In some embodiments, the topoisomerase inhibitor is doxorubicin.

**[0048]** In some embodiments, the third chemotherapeutic agent comprises an alkylating agent.

**[0049]** In some embodiments, the alkylating agent is cyclophosphamide.

**[0050]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1 and 8.

**[0051]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15.

**[0052]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15, and 22.

**[0053]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15, 22, and 28.

**[0054]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, and 22.

**[0055]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 5 days.

**[0056]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 6 days.

**[0057]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 7 days.

**[0058]** In some embodiments, the periodic administration comprises at least 2 cycles.

**[0059]** In some embodiments, the periodic administration comprises at least 5 cycles.

**[0060]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and the third chemotherapeutic agent are administered on the same day and subsequently the administration of the chemotherapeutic agent associated with or bound to albumin is repeated for a plurality of cycles.

**[0061]** In some embodiments, the plurality of cycles for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least 2 cycles.

**[0062]** In some embodiments, the plurality of cycles for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least 5 cycles.

**[0063]** In some embodiments, each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 5 days.

**[0064]** In some embodiments, each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 6 days.

**[0065]** In some embodiments, each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 7 days.

**[0066]** In some embodiments, each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 1 week.

**[0067]** In some embodiments, at least about 100 mg/m$^2$ Abraxane is administered on day 1 and 8, at least about 50 mg/m$^2$ doxorubicin is administered on day 1, and at least about 500 mg/m$^2$ cyclophosphamide is administered on day 1.

**[0068]** Some embodiments also include administering Pegfilgrastim on day 9.

**[0069]** In some embodiments, the cancer is breast cancer.

**[0070]** In some embodiments, the cancer is HER2 negative breast cancer.

**[0071]** In some embodiments, the cancer is triple negative breast cancer.

**[0072]** In some embodiments, the dose of Abraxane is between about 50 mg/m$^2$ and about 200 mg/m$^2$.

**[0073]** In some embodiments, the dose of Abraxane is selected from the group consisting of 100 mg/m$^2$ and 150 mg/m$^2$.

## DETAILED DESCRIPTION

**[0074]** The present invention relates to methods and compositions for the treatment of cancer. Some embodiments include methods of treating cancer comprising administering a chemotherapeutic agent associated with or bound to albumin, administering a second chemotherapeutic agent; and administering a third chemotherapeutic agent.

**[0075]** Currently, there is no cure for patients with metastatic breast cancer. Therefore, treating patients with early stage breast cancer, either before surgery (neoadjuvant) or after surgery (adjuvant) is an important strategy to reduce the chance of cancer recurrence locally or distally, thereby reducing morbidity and mortality.

**[0076]** Triple-negative breast cancer includes breast cancers that do not express the genes for estrogen receptor (ER), progesterone receptor (PR) or Her2/neu. This subtype of breast cancer is clinically characterized as more aggressive and less responsive to standard treatment and associated poorer overall patient prognosis. Basal-like or triple negative breast cancer cells express high levels of Secreted protein, acidic, cysteine-rich (SPARC) protein, also known as osteonectin, which binds and entraps albumin. Overexpression of SPARC protein has also been reported in many human cancers such as, prostate and colon cancers.

**[0077]** Expression of SPARC protein by cancer cells can be useful to target chemotherapeutic agents to a tumor. In an example pathway, activation of a specific receptor (gp60) on the endothelial cell wall in turn activates the protein, caveolin-1. Caveolin-1 can initiate the formation of caveolae which can transport materials, such as chemotherapeutic agents associated with albumin to the tumor interstitium (17). SPARC protein expressed by the tumor may bind and entrap the chemotherapeutic agents associated with or bound to albumin (18). Abraxane is an example of a chemotherapeutic agent associated with albumin.

**[0078]** There is currently no clear recommendation on neoadjuvant chemotherapy regimens. Doxorubicin (Adriamycin) and taxanes are active drugs against breast cancer. A regimen of Taxotere, Adriamycin, and Cyclophosphamide (TAC) administered every three weeks for 6 cycles, is among the most active regimens in the adjuvant and neoadjuvant settings (3, 13, 14). However, the pathologic complete response rate, which is a surrogate for long term survival, is quite low for this regimen. A regimen of Abraxane administered weekly can provide an increased positive response in patients with lower side effects, compared to a regimen of administering Taxotere every 3 weeks. Some methods described herein include regimens including administration of Nab-paclitaxel, Adriamycin, and Cytoxan (NAC).

**[0079]** The TAC regimen (docetaxel, doxorubicin, and cyclophosphamide) is among the most active drug combinations in the adjuvant and neoadjuvant settings. A weekly *nab*-paclitaxel is superior to every-three week docetaxel in both efficacy and toxicity in patients with metastatic breast cancer. Provided herein are results of a single center phase I study in which *nab*-paclitaxel replaces docetaxel in the conventional TAC regimen.

Albumin-associated or albumin-bound chemotherapeutic agents

**[0080]** Some embodiments of the methods and compositions described herein include chemotherapeutic agents associated with or bound to albumin. Examples of chemotherapeutic agents which may be associated with or bound to albumin include Vinca alkaloids (e.g., Vinblastine, Vincristine, Vinflunine, Vindesine, Vinorelbine) Taxanes (e.g., Cabazitaxel, Docetaxel, Larotaxel, Ortataxel, Paclitaxel, Tesetaxel) and Epothilones (e.g., Ixabepilone), dihydrofolate reductase inhibitors (e.g., Aminopterin, Methotrexate, Pemetrexed, Pralatrexate), thymidylate synthase inhibitors (e.g., Raltitrexed, Pemetrexed), adenosine deaminase inhibitors (e.g., Pentostatin), ribonucleotide reductase inhibitors (e.g., Cladribine, Clofarabine, Fludarabine), thiopurine (e.g., Thioguanine, Mercaptopurine), thymidylate synthase inhibitors (e.g., Fluorouracil, Capecitabine, Tegafur, Carmofur, Floxuridine), DNA polymerase inhibitors (e.g., Cytarabine), ribonucleotide reductase inhibitors (e.g., Gemcitabine),

hypomethylating agents (e.g., Azacitidine, Decitabine), ribonucleotide reductase inhibitors (e.g., Hydroxycarbamide), Topoisomerase inhibitors (e.g., Camptothecin, Topotecan, Irinotecan, Rubitecan, Belotecan, Etoposide, Teniposide, Anthracyclines such as Aclarubicin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Valrubicin, Zorubicin, and Anthracenediones such as Mitoxantrone, Pixantrone), Alkylating agents (e.g., Mechlorethamine, Cyclophosphamide such as Ifosfamide and Trofosfamide, Chlorambucil such as Melphalan, Prednimustine, as well as Bendamustine, Uramustine, Nitrosoureas such as Carmustine, Lomustine, Fotemustine, Nimustine. Ranimustine. Streptozocin, Alkyl sulfonates such as Busulfan, Mannosulfan, and Treosulfan, and Aziridines such as Carboquone, ThioTEPA, Triaziquone, and Triethylenemelamine), Platinums (e.g., Carboplatin, Cisplatin, Nedaplatin, Oxaliplatin, Triplatin tetranitrate, and Satraplatin), Hydrazines (e.g., Procarbazine), Triazenes (e.g., Dacarbazine, Temozolomide), Altretamine, and Mitobronitol, Intercalation agents (e.g., Actinomycin, Bleomycin, Mitomycin, Plicamycin). More examples of chemotherapeutic agents include Aminolevulinic acid, Efaproxiral, Porphyrin derivatives (e.g., Porfimer sodium, Talaporfin, Temoporfin, Verteporfin), Enzyme inhibitors (e.g., Tipifarnib, Alvocidib, Seliciclib, Bortezomib, Anagrelide, Tiazofurine, Masoprocol, Olaparib, Vorinostat, Romidepsin), Atrasentan, Bexarotene, Testolactone, Amsacrine, Trabectedin, Alitretinoin, Tretinoin, Arsenic trioxide, Celecoxib, Demecolcine, Elesclomol, Elsamitrucin, Etoglucid, Lonidamine, Lucanthone, Mitoguazone, Mitotane, Oblimersen, Omacetaxine mepesuccinate, Everolimus, and Temsirolimus.

**[0081]** In some embodiments, the chemotherapeutic agent and albumin comprise a nanoparticle. Examples nanoparticle include Nab-paclitaxel (Abraxane®). Abraxane is a novel biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. Abraxane is an example of an interactive nanoparticle leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic drug in normal tissue.

**[0082]** In some embodiments of the methods and uses provided herein, two or more of the chemotherapeutic agents described herein can be administered to a subject in need thereof. In some embodiments, three or more of the chemotherapeutic agents described herein can be administered to a subject in need thereof. In some such embodiments, at least one of the chemotherapeutic agents administered to the subject comprises a chemotherapeutic agent associated with or bound to albumin.

Preclinical and Clinical Studies with Abraxane

**[0083]** Preclinical studies comparing Abraxane to Taxol demonstrated lower toxicities, with a maximum tolerated dose (MTD) approximately 50% higher for Abraxane compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, Abraxane was found to be markedly more efficacious than Taxol (19).

Every 3 Weeks Schedule

**[0084]** In a phase I study, the MTD of Abraxane was determined to be 300 mg/m$^2$ by 30 minute infusion every 3 weeks, without premedication or G-CSF support (20). No severe hypersensitivity reactions occurred with Abraxane despite the absence of premedication. Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m$^2$.

**[0085]** Two multicenter phase II studies have evaluated 2 dose levels of Abraxane (300 mg/m$^2$, n=63, and 175 mg/m$^2$, n=43) in patients with metastatic breast cancer (21, 22). The overall response rates in these 2 phase II trials were 40% (95% CI 25-54%) for the 175 mg/m$^2$ dose, and 48% (95% CI 35-60%) for the 300 mg/m$^2$ dose. Of 39 patients receiving 300 mg/m$^2$ as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded. This was contrasted with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly.

**[0086]** A Phase III trial in patients with metastatic breast cancer compared Abraxane 260 mg/m$^2$ to Taxol 175 mg/m$^2$ given every 3 weeks (23). Efficacy analyses were based on the intent-to-treat (ITT) population. The overall response rate (ORR) was significantly greater for Abraxane than for Taxol for all patients (33% v 19%, respectively; P = 0.001), patients who received first-line therapy (42% v 27%, respectively; P = 0.029), patients who received second-line or greater therapy (27% v 13%, respectively; P = 0.006), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% v 18%, respectively; P = 0.002) or the metastatic setting only (27% v 14%, respectively; P = 0.010). Tumor response rate was also significantly higher for Abraxane than for Taxol in patients with visceral dominant lesions (34% v 19%, respectively; P = 0.002) and in patients aged younger than 65 years (34% v 19%, respectively; P < 0.001). ORR also was greater for Abraxane compared with standard paclitaxel in patients with nonvisceral dominant lesions (34% v 19%, respectively) and in

patients ≥ 65 years old (27% v 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets.

**[0087]** Median time to tumor progression (TTP) was significantly longer with Abraxane than with Taxol for all patients (23.0 v 16.9 weeks, respectively; hazard ratio [HR] = 0.75; P = 0.006). There was a trend for greater median survival for all patients treated with Abraxane than with Taxol (65.0 v 55.7 weeks, respectively; P = 0.374). Although no difference in survival was observed in first-line patients, the difference was statistically significant in patients who received Abraxane, compared with Taxol, as second-line or greater therapy (56.4 v 46.7 weeks, respectively; HR = 0.73; P = .024) (23).

**[0088]** The incidence of hypersensitivity reactions (any grade) was low for both arms (1% for Abraxane and 2% for Taxol). No severe (grade 3 or 4) treatment-related hypersensitivity reactions occurred in any of the patients in the Abraxane group despite the absence of premedication. In contrast, grade 3 hypersensitivity reactions occurred in the Taxol group despite standard premedication (chest pain, two patients; allergic reaction, three patients). Per protocol, corticosteroids and antihistamines were not administered routinely to patients in the Abraxane group; however, premedication was administered for emesis, myalgia/arthralgia, or anorexia in 18 patients (8%) in the Abraxane group in 2% of the treatment cycles, whereas 224 patients (> 99%) in the Taxol group received premedication in 95% of the cycles.

**[0089]** Although the patients in the Abraxane group received an average paclitaxel dose-intensity 49% greater than that received by patients in the Taxol group, the incidence of treatment-related grade 4 neutropenia was significantly lower in the Abraxane group than in the Taxol group (9% v 22%, respectively; P < 0.001), with a higher mean neutrophil nadir (1.67 v $1.31 \times 10^9$/L, respectively; P = 0.046), suggesting that polyethylated castor oil may have contributed to this toxicity in patients who received standard paclitaxel.

**[0090]** As expected with a higher dose of paclitaxel, treatment-related grade 3 sensory neuropathy occurred more frequently in the Abraxane arm than in the Taxol arm (10% v 2%, respectively; P < 0.001); however, these episodes improved with interruption of treatment to grade 2 or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction. By day 28 after its first occurrence, the number of patients with persistent grade 3 sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group.

**[0091]** The only clinical chemistry value that was notably different between the two treatment arms was higher serum glucose levels in the Taxol–treated patients, who also had a

higher incidence of hyperglycemia reported as an adverse effect (AE) compared with Abraxane–treated patients (7% v 1% respectively; P =0.003).

**[0092]** Subgroup analyses revealed that the safety profiles of Abraxane and Taxol in patients who received the drugs as first-line therapy were similar to those in the overall study population. In subgroup analyses by age, the reported AEs were similar in patients less than 65 years old and patients ≥ 65 years old in both groups. Of the patients ≥ 65 years old, the incidences of the following AEs were notably lower in the Abraxane group than in the Taxol group: neutropenia (23% v 59%, respectively), leukopenia (10% v 31%, respectively), nausea (20% v 38%, respectively), hyperglycemia (0% v 19%, respectively), and flushing (0% v 16%, respectively). These data indicate no additional safety concerns for Abraxane in patients ≥ 65 years old compared with younger patients.

**[0093]** Six patients (3%) in the Abraxane group and eight patients (4%) in the standard paclitaxel group died during the study, all as a result of disease progression. No treatment-related deaths occurred in the Abraxane group; one patient (< 1%) in the Taxol group died of multiorgan failure, which was considered by the investigator to be possibly related to treatment but may also have been a result of sepsis and/or progressive disease.

Weekly for 3 Weeks, Every 4 Weeks Schedule

**[0094]** Thirty-nine patients were enrolled into A Phase I study of Abraxane administered weekly for 3 weeks followed by a 1 week rest in patients with advanced solid tumors (24). The MTDs for heavily and lightly pre-treated patients were 100 and 150 mg/m2 respectively. Dose limiting toxicities included grade 4 neutropenia and grade 3 sensory neuropathy. Premedication was not required, and unexpected, non-taxane associated toxicities were not observed.

**[0095]** In a Phase II trial in heavily pretreated patients with taxane-refractory metastatic breast cancer, objective antitumor responses occurred in 15% of women treated with Abraxane 100 mg/m2 on this schedule (25). Abraxane weekly regimen was well tolerated. 91% of patients were treated at the full dose of 100 mg/m2 of Abraxane without dose reductions. Based on the activity and low toxicity documented with the Abraxane 100 mg/m2 weekly regimen, this study was expanded to evaluate the efficacy and safety/tolerability of a higher dose of Abraxane 125 mg/m$^2$ weekly regimen in 75 additional patients. Results of this dose-finding study confirm the dose of Abraxane 100 mg/m$^2$ as the appropriate dose for further study in this patient population (26).

Weekly Schedule

**[0096]** The NSABP studied the administration of Abraxane in a neoadjuvant setting to patients with locally advanced breast cancer at a dose of 100 mg/m$^2$ weekly for 12 weeks, with no break (27). Four cycles of FEC were administered sequentially based on patients' HER2 status: HER2 negative patients received FEC-100 (F: 500 mg/m$^2$, E: 100 mg/m$^2$, C: 500 mg/m$^2$ Q3 weeks) and HER2 positive patients received weekly trastuzumab in addition to FEC-75 (F: 500 mg/m$^2$, E: 75 mg/m$^2$, C: 500 mg/m$^2$ Q3 weeks). Weekly trastuzumab was permitted during Abraxane and FEC-75 treatment at the discretion of the investigator. The primary objective of the trial was to determine the pathologic complete response rate (pCR) in the breast. At the time of initial report at SABCS 2006, 65 patients had been entered on study and were evaluable for cCR and safety. Following 12 weeks of Abraxane, a clinical complete response rate (cCR) of 32% was noted. The therapy was well tolerated, with 48/65 patients receiving 12 doses in 12 weeks and 13/65 receiving 12 doses in 13-14 weeks. The incidence of peripheral (sensory) neuropathy was low (11% grade 2 and 5% grade 3) as was neutropenia (3% grade 3 and no grade 4). The authors concluded that the administration of Abraxane 100 mg/m$^2$ weekly x 12 was both effective and tolerable.

**[0097]** A recent phase II study has also demonstrated that weekly Abraxane is superior to every-three week Taxotere in both efficacy and toxicity profile, in the treatment of patients with advanced or metastatic breast cancer (28). The rate of grade 4 neutropenia was 75% in the Taxotere group, compared to only 5% of the weekly Abraxane groups. Therefore, the use of growth factor support such as Neulasta that is often employed upfront in the TAC regimen (Taxotere, Adriamycin, Cyclophosphamide) may be omitted or reduced when Taxotere is replaced by Abraxane. This may also help reduce the toxicity and overall cost of treatments (Neulasta is an expensive drug and adds considerably to the cost of treatments).

Commercial Chemotherapy

**[0098]** Doxorubicin and cyclophosphamide are commercially available drugs that are commonly used in the treatment of breast cancer. *See e.g.*, the *Physicians' Desk Reference*, incorporated herein by reference in its entirety.

Method for treating cancer

**[0099]** Some embodiments include methods of treating a cancer in a subject in need thereof. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is HER2 negative breast cancer. In some embodiments, the cancer is triple negative breast cancer.

Some such methods include administering a chemotherapeutic agent associated with or bound to albumin, administering a second chemotherapeutic agent; and administering a third chemotherapeutic agent. In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered periodically. In some embodiments, the chemotherapeutic agent associated with or bound to albumin comprises an agent selected from the group consisting of paclitaxel, docetaxel, and rapamycin. In particular embodiments, the chemotherapeutic agent associated with or bound to albumin is Abraxane.

**[0100]** In some embodiments, the second chemotherapeutic agent comprises a topoisomerase inhibitor. Examples of topoisomerase inhibitors are described herein and can include doxorubicin. In some embodiments, the third chemotherapeutic agent comprises an alkylating agent. Examples of alkylating agents are described herein and can include cyclophosphamide.

**[0101]** In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered on days 1 and 8, or on days 1, 8, 15, or on days 1, 8, 15, and 22, or on days 1, 8, 15, 22, and 28, or on days 1, 8, and 22. In some embodiments, the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 7 days, at least about 8 days, at least about 9 days, and at least about 10 days. In some embodiments, the administration of the chemotherapeutic agent associated with or bound to albumin; the administration of the second chemotherapeutic agent; and/or the administration of the third chemotherapeutic agent are repeated for a plurality of cycles. In some embodiments, the plurality of cycles is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 cycles.

**[0102]** In some embodiments, the dose of a chemotherapeutic agent associated with or bound to albumin, such as Abraxane, is between about 50 $mg/m^2$ and about 200 $mg/m^2$. In some embodiments, the dose of a chemotherapeutic agent associated with or bound to albumin, such as Abraxane, is selected from the group consisting of about 100 $mg/m^2$ and about 150 $mg/m^2$.

**[0103]** In some embodiments, at least about 100 $mg/m^2$ Abraxane is administered on day 1 and 8, at least about 50 $mg/m^2$ doxorubicin is administered on day 1, and at least about 500 $mg/m^2$ cyclophosphamide is administered on day 1. Some such embodiments also include, administering Pegfilgrastim. In some embodiments, Pegfilgrastim is administered on day 9.

EXAMPLES

Example 1 – Phase I Study of Neoadjuvant Chemotherapy with Nanoparticle Albumin Bound Paclitaxel, Doxorubicin, and Cyclophosphamide

**[0104]** A Phase I study of neoadjuvant chemotherapy with nanoparticle albumin bound paclitaxel, doxorubicin, and cyclophosphamide (NAC) in patients with stages II-III HER-2 negative breast cancer was carried out.

**[0105]** Background: The TAC regimen (docetaxel, doxorubicin, and cyclophosphamide) is among the most active drug combinations in the adjuvant and neoadjuvant settings. A weekly *nab*-paclitaxel is superior to every-three week docetaxel in both efficacy and toxicity in patients with metastatic breast cancer. Provided herein are results of a single center phase I study in which *nab*-paclitaxel replaces docetaxel in the conventional TAC regimen.

**[0106]** Methods: Women with HER-2 negative stages II-III breast cancer were enrolled. Eligible patients received 6 cycles of the NAC regimen: *nab*-paclitaxel (100-150 mg/m$^2$, days 1 and 8), doxorubicin (50 mg/m$^2$, day 1), and cyclophosphamide (500 mg/m$^2$, day 1). Peg-filgrastim was given on day 9. Table 1 shows Abraxane dose schedules.

TABLE 1

| Dose level | Abraxane dose (mg/m$^2$) | Dose schedule (days) |
|---|---|---|
| -1 | 100 | 1, 8, rest |
| 0 | 100 | 1, 8, 15, 22, 29, rest |
| 1 | 150 | 1, 8, rest, 22, 29, rest |
| 2 | 150 | 1, 8, 15, 22, 29, rest |

**[0107]** Results: Sixteen patients enrolled in the study, one of which was a screen failure. Median tumor size was 6 cm. Median age was 54 years (40-69). ER+ tumors accounted for 53%, and 47% were triple negative. There were two inflammatory breast cancers. After the first three patients on dose level 0 (nab-paclitaxel of 100 mg/m$^2$, weekly 5 on 1 off, Q 6 weeks) experienced several dose delays because of grades 3 and 4 neutropenia, the protocol was amended such that dose level -1 (nab-paclitaxel of 100 mg/m$^2$, weekly 2 on 1 off, Q 3 weeks) would be the new starting point and there would be no further dose escalation. There was no dose limiting toxicity (DLT). To date, a total of 57 cycles of dose level -1 were given. 43.8% required dose delay. There were two episodes of febrile neutropenia. The pathologic complete response (pCR) by physical examination was 93.3%. One patient had a minimal response. The median number of cycles required before a pCR was 2. Even though pCR was not a primary end

point, we observed a very favorable pCR rate. Eight patients already underwent surgery. The pCR rate for this group was 50%. Another patient had a near pCR, with microscopic residual disease. The pCR for the 4 triple negative patients was 100%.

**[0108]** Conclusions: This single center phase I study demonstrated safety and dramatic activity for the neoadjuvant NAC regimen in patients with stages II-III HER-2 negative breast cancer. This regimen was highly effective with impressive clinical and pathologic complete responses.

Example 2 – Determination of dosage regimens

**[0109]** Other dosage regimens for chemotherapy with a combination of two or more of the chemotherapeutic agents described herein, such as nanoparticle albumin bound paclitaxel, doxorubicin, and/or cyclophosphamide (NAC), can be tested in patients, such as patients with stages II-III HER-2 negative breast cancer. A series of studies are carried out with a combination of different chemotherapeutic agents. In each study, the period of providing a particular chemotherapeutic agent is different, for example, the particular chemotherapeutic agent is periodically administered to a patient at an interval of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, or 10 days, or 1 week, 2 weeks, 3 weeks, or 4 weeks. The pCR for each study group is determined.

**[0110]** Likewise, the period of providing the second and/or third chemotherapeutic agent may be varied and the second and/or third chemotherapeutic agents may be administered simultaneously with, on the same day as, or on a different day as the first or second chemotherapeutic agent in order to identify a treatment regimen that provides desirable results. In addition, regimens in which one or more of the chemotherapeutic agents are administered one or more times and the subsequent administrations of those chemotherapeutic agents discontinued while administration of the remaining one or more chemotherapeutic agents is continued may be evaluated to identify regimens that provide desirable results.

**[0111]** Using particular regimens, the pCR is at least 30%, 40, 50%, 60%, 70%, 80%, 90% or 95%. The optimum period for providing the particular chemotherapeutic agent in combination with at least one other chemotherapeutic agent is determined.

**[0112]** The above description discloses several compositions and methods of the present invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the

specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention.

**[0113]** All references cited herein including, but not limited to, published and unpublished applications, patents, and literature references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

**[0114]** The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

**[0115]** The following references are incorporated herein by reference in their entireties.

REFERENCES

1. American Cancer Society: Cancer Facts and Figures 2007. Atlanta: American Cancer Society; 2007.
2. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997 Jul;15(7):2483-93.
3. von Minckwitz G, Blohmer JU, Raab G, Löhr A, Gerber B. In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study. Ann Oncol. 2005 Jan;16(1):56-63.
4. Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, Brown AM, Robidoux A, Margolese R, Kahlenberg MS, Paik S, Soran A, Wickerham DL, Wolmark N. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2006 May 1;24(13):2019-27.
5. Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, Ah-See AK, Eremin O, Walker LG, Sarkar TK, Eggleton SP, Ogston KN. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol. 2002 Mar 15;20(6):1456-66.
6. Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. Br J Surg. 2007 Oct;94(10):1189-200.
7. Norman Wolmark, M.D., "Preoperative Therapy in Invasive Breast Cancer: Reviewing the State of the Science and Exploring New Research Directions," National Cancer Institute, Natcher Conference Center, Bethesda, Maryland, March 26-27, 2007.
8. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol. 2001 Nov 15;19(22):4224-37.
9. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr. 2001;(30):96-102.

10. Cleator SJ, Makris A, Ashley SE, Lal R, Powles TJ. Good clinical response of breast cancers to neoadjuvant chemoendocrine therapy is associated with improved overall survival. Ann Oncol. 2005 Feb;16(2):267-72.
11. Semiglazov VF, Topuzov EE, Bavli JL, Moiseyenko VM, Ivanova OA, Seleznev IK, Orlov AA, Barash NY, Golubeva OM, Chepic OF. Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer. Ann Oncol. 1994 Sep;5(7):591-5.
12. Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, Blohmer JU, Eiermann W, Jackesz R, Jonat W, Lebeau A, Loibl S, Miller W, Seeber S, Semiglazov V, Smith R, Souchon R, Stearns V, Untch M, von Minckwitz G. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol. 2006 Apr 20;24(12):1940-9. Erratum in: J Clin Oncol. 2006 Jul 1;24(19):3221.
13. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C, Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005 Jun 2;352(22):2302-13.
14. G. Von Minckwitz, J. Blohmer, P. Vogel, C. Hanusch, H. Eidtmann, J. Hilfrich, B. Gerber, J. Huober, S. Costa and M. Kaufmann. Comparison of neoadjuvant 6 vs 8 cycles of docetaxel/doxorubicin/cyclophosphamide (TAC) in patients early responding to TACx2-the GEPARTRIO Study. Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition). No 18S (June 20 Supplement), 2006: 576
15. Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky EK, Wood WC. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 2003 Feb 15;21(4):588-92.
16. Mazouni C, Kau SW, Frye D, Andre F, Kuerer HM, Buchholz TA, Symmans WF, Anderson K, Hess KR, Gonzalez-Angulo AM, Hortobagyi GN, Buzdar AU, Pusztai L. Inclusion of taxanes, particularly weekly paclitaxel, in preoperative chemotherapy improves pathologic complete response rate in estrogen receptor-positive breast cancers. Ann Oncol. 2007 May;18(5):874-80.
17. Desai N, Trieu V, Yao R, Labao E, Soon-Shiong P: Increased endothelial transcytosis of nanoparticle albumin-bound paclitaxel (ABI-007) by gp60-receptors: a pathway inhibited by taxol. 2004 SABCS. Abstract No. 1071.
18. Desai N, Trieu V, Yao R, Frankel T, Soon-Shiong P: SPARC expression in breast tumors may correlate to increased tumor distribution of nanoparticle albumin-bound paclitaxel (ABI-007) vs taxol. 2004 SABCS. Abstract No. 206.
19. Desai N, Trieu V, Yao Z, et al: Increased Antitumor Activity, Intratumor Paclitaxel Concentrations and Endothelial Cell Transport of Cremophor-Free, Albumin-Bound Paclitaxel, ABI-007, Compared with Cremophor-Based Paclitaxel. Clin Cancer Res. 2006; 12(4). 1317-1324.
20. Ibrahim NK, Desai N, Legha S, et al: Phase I and Pharmacokinetic Study of ABI-007, a Cremophor-free, Protein-stabilized, Nanoparticle Formulation of Paclitaxel. Clin Cancer Research. 2002 May; 8: 1038-1044
21. Ibrahim NK, Samuels B, Page R, et al: Multicenter Phase II Trial of ABI-007, an Albumin-Bound Paclitaxel, in Women with Metastatic Breast Cancer. J Clin Oncol 23:6019-6026, 2005.
22. Investigator's Brochure. Abraxane® (Paclitaxel Albumin Nanoparticle for Injectable Suspension) (ABI-007). American BioScience, Inc.
23. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Hawkins M, O'Shaughnessy J. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005 23(31):7794-803

24. Nyman DW, Campbell KJ, Hersh, E, et al: Phase I and Pharmacokinetics Trial of ABI-007, a Novel Nanoparticle Formulation of Paclitaxel in Patients with Advanced Nonhematologic Malignancies. J Clin Oncol 23:7785-7793, 2005
25. Blum JL, et al: Long-term Disease Control in Taxane-Refractory Metastatic Breast Cancer Treated with nab paclitaxel. 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: Abstract No. 543.
26. OShaughnessy JA, Blum JL, Sandbach JF, et al: Weekly Nanoparticle Albumin Paclitaxel (Abraxane) Results in Long-Term Disease Control in Patients with Taxane-Refractory Metastatic Breast Cancer. 2004 SABCS. Abstract No. 1070
27. Robidoux A, Buyse M, Buzdar A, et al. Neoadjuvant chemotherapy with sequential weekly nanoparticle albumin-bound paclitaxel (ABI-007, Abraxane®) followed by 5-fluorouracil, epirubicin and cyclophosphamide (FEC) in locally advanced breast cancer (LABC): a phase II trial of the NSABP Foundation research programs (FRP) [poster]. Presented at: San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, TX. Abs 3068.
28. Gradishar W, Krasnojon D, Cheporov S, et al. Randomized comparison of weekly or every-3-week (q3w) nab-paclitaxel compared to q3w docetaxel as first-line therapy in patients (pts) with metastatic breast cancer (MBC). J Clin Oncol, 2007 ASCO Annual Meeting Proceedings. 25 (18S) (June 20 Supplement), 2007: 1032

WHAT IS CLAIMED IS:

1. A method of treating a cancer in a subject in need thereof comprising:

administering a chemotherapeutic agent associated with or bound to albumin;

administering a second chemotherapeutic agent; and

administering a third chemotherapeutic agent.

2. The method of claim 1, wherein the chemotherapeutic agent associated with or bound to albumin is administered periodically.

3. The method of any one of claims 1 or 2, wherein the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and a third chemotherapeutic agent are administered on the same day and subsequently the chemotherapeutic agent associated with or bound to albumin is administered periodically without the second chemotherapeutic agent and the third chemotherapeutic agent.

4. The method of any one of claims 1 or 2, wherein on some occasions the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and a third chemotherapeutic agent are administered on the same day and on other occasions only the chemotherapeutic agent associated with or bound to albumin is administered.

5. The method of any one of claims 1-4, wherein the chemotherapeutic agent associated with or bound to albumin comprises an agent selected from the group consisting of paclitaxel, docetaxel, and rapamycin.

6. The method of any one of claims 1-4, wherein the chemotherapeutic agent associated with or bound to albumin is Abraxane.

7. The method of any one of claims 1-4, wherein the second chemotherapeutic agent comprises a topoisomerase inhibitor.

8. The method of claim 7, wherein the topoisomerase inhibitor is doxorubicin.

9. The method of any one of claims 1-8, wherein the third chemotherapeutic agent comprises an alkylating agent.

10. The method of claim 9, wherein the alkylating agent is cyclophosphamide.

11. The method of any one of claims 1-10, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1 and 8.

12. The method of any one of claims 1-10, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15.

13. The method of any one of claims 1-10, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15, and 22.

14. The method of any one of claims 1-10, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15, 22, and 28.

15. The method of any one of claims 1-10, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, and 22.

16. The method of any one of claims 1-10, wherein the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 5 days.

17. The method of any one of claims 1-10, wherein the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 6 days.

18. The method of any one of claims 1-10, wherein the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 7 days.

19. The method of any one of claim 2-10, wherein the periodic administration comprises at least 2 cycles.

20. The method of any one of claim 2-10, wherein the periodic administration comprises at least 5 cycles.

21. The method of claim 3, wherein the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and the third chemotherapeutic agent are administered on the same day and subsequently the administration of the chemotherapeutic agent associated with or bound to albumin is repeated for a plurality of cycles.

22. The method of claim 21, wherein the plurality of cycles for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least 2 cycles.

23. The method of claim 21, wherein the plurality of cycles for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least 5 cycles.

24. The method of claim 21, wherein each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 5 days.

25. The method of claim 21, wherein each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 6 days.

26. The method of claim 21, wherein each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 7 days.

27. The method of claim 21, wherein each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 1 week.

28. The method of claim 1, wherein at least about 100 mg/m$^2$ Abraxane is administered on day 1 and 8, at least about 50 mg/m$^2$ doxorubicin is administered on day 1, and at least about 500 mg/m$^2$ cyclophosphamide is administered on day 1.

29. The method of claim 28, further comprising administering Pegfilgrastim on day 9.

30. The method of any one of claims 1-29, wherein said cancer is breast cancer.

31. The method of any one of claims 1-29, wherein the cancer is HER2 negative breast cancer.

32. The method of any one of claims 1-29, wherein the cancer is triple negative breast cancer.

33. The method of claim 6, wherein the dose of Abraxane is between about 50 mg/m$^2$ and about 200 mg/m$^2$.

34. The method of claim 6, wherein the dose of Abraxane is selected from the group consisting of 100 mg/m$^2$ and 150 mg/m$^2$.

35. Use of a combination comprising a chemotherapeutic agent associated with or bound to albumin, a second chemotherapeutic agent, and a third chemotherapeutic agent for the treatment of cancer.

36. The use of claim 35, wherein the chemotherapeutic agent associated with or bound to albumin is administered periodically.

37. The use of any one of claims 35 or 36, wherein the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and a third chemotherapeutic agent are administered on the same day and subsequently the chemotherapeutic agent associated with or bound to albumin is administered periodically without the second chemotherapeutic agent and the third chemotherapeutic agent.

38. The use of any one of claims 35 or 36, wherein on some occasions the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and a third chemotherapeutic agent are administered on the same day and on other occasions only the chemotherapeutic agent associated with or bound to albumin is administered.

39. The use of any one of claims 35-38, wherein the chemotherapeutic agent associated with or bound to albumin comprises an agent selected from the group consisting of paclitaxel, docetaxel, and rapamycin.

40. The use of any one of claims 35-38, wherein the chemotherapeutic agent associated with or bound to albumin is Abraxane.

41. The use of any one of claims 35-38, wherein the second chemotherapeutic agent comprises a topoisomerase inhibitor.

42. The use of claim 41, wherein the topoisomerase inhibitor is doxorubicin.

43. The use of any one of claims 35-42, wherein the third chemotherapeutic agent comprises an alkylating agent.

44. The use of claim 43, wherein the alkylating agent is cyclophosphamide.

45. The use of any one of claims 35-44, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1 and 8.

46. The use of any one of claims 35-44, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15.

47. The use of any one of claims 35-44, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15, and 22.

48. The use of any one of claims 35-44, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, 15, 22, and 28.

49. The use of any one of claims 35-44, wherein the chemotherapeutic agent associated with or bound to albumin is administered on days 1, 8, and 22.

50. The use of any one of claims 35-44, wherein the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 5 days.

51. The use of any one of claims 35-44, wherein the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 6 days.

52. The use of any one of claims 35-44, wherein the chemotherapeutic agent associated with or bound to albumin is administered at an interval of at least about 7 days.

53. The use of any one of claim 36-44, wherein the periodic administration comprises at least 2 cycles.

54. The use of any one of claim 36-44, wherein the periodic administration comprises at least 5 cycles.

55. The use of claim 37, wherein the chemotherapeutic agent associated with or bound to albumin the second chemotherapeutic agent and the third chemotherapeutic agent are administered on the same day and subsequently the administration of the chemotherapeutic agent associated with or bound to albumin is repeated for a plurality of cycles.

56. The use of claim 55, wherein the plurality of cycles for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least 2 cycles.

57. The use of claim 55, wherein the plurality of cycles for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least 5 cycles.

58. The use of claim 55, wherein each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 5 days.

59. The use of claim 55, wherein each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 6 days.

60. The use of claim 55, wherein each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 7 days.

61. The use of claim 55, wherein each cycle for the subsequent administration of the chemotherapeutic agent associated with or bound to albumin comprises at least about 1 week.

62. The use of claim 35, wherein at least about 100 $mg/m^2$ Abraxane is administered on day 1 and 8, at least about 50 $mg/m^2$ doxorubicin is administered on day 1, and at least about 500 $mg/m^2$ cyclophosphamide is administered on day 1.

63. The use of claim 62, further comprising administering Pegfilgrastim on day 9.

64. The use of any one of claims 35-63, wherein said cancer is breast cancer.

65. The use of any one of claims 35-63, wherein the cancer is HER2 negative breast cancer.

66. The use of any one of claims 35-63, wherein the cancer is triple negative breast cancer.

67. The use of claim 40, wherein the dose of Abraxane is between about 50 $mg/m^2$ and about 200 $mg/m^2$.

68. The use of claim 40, wherein the dose of Abraxane is selected from the group consisting of 100 $mg/m^2$ and 150 $mg/m^2$.