TMHRI IRB# 0811-0147

CAT Trial

PHASE II STUDY OF THE EFFICACY AND SAFETY OF CHLOROQUINE (C) IN COMBINATION WITH TAXANE OR TAXANE-LIKE (T) CHEMO AGENTS IN THE TREATMENT OF PATIENTS WITH ADVANCED OR METASTATIC BREAST CANCER WHO HAVE FAILED ANTHRACYCLINE BASED CHEMOTHERAPY.

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PHASE: II

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STUDY SUMMARY

Title:	Phase II Study of The Efficacy And Safety of Chloroquine (C) in CombinAtion With Taxane or Taxane-like (T) Chemo Agents in The Treatment of Patients With Advanced or Metastatic Breast Cancer Who Have Failed Anthracycline Chemo Base Therapy.
Objectives:	The primary objective: To determine the anti-tumor activity of the combination of Chloroquine + Taxane or Taxane-like chemo agents (Paclitaxel, Docetaxel, Abraxane, Ixabepilone) (C/T) measured by Overall Response Rate (ORR). The secondary objective(s): • To assess the safety and tolerability of the combination of C/T • To assess the response rate and tumor control rate (TCR) of patients receiving C/T • To assess the Time to Progression (TTP) of patients receiving C/T. • To assess the duration of response (DOR) of patients receiving C/T. Exploratory Objective(s): • To evaluate biomarkers for response and toxicity of the combination of C/T.
Study Population:	Patients with advanced or metastatic breast cancer, who have failed anthracycline based chemotherapy.
Sample Size:	47 patients
Number of Centers:	Single Institution: The Methodist Hospital Research Institute. Weill Cornell Medical College
Treatment Plan:	This is a phase II trial; 47 patients with diagnosis of advanced or metastatic breast cancer, who have failed anthracycline based therapy, will be enrolled in the study. Patients will receive Chloroquine (C) together with Taxane or Taxane-like (Paclitaxel, Docetaxel, Abraxane, Ixabepilone) (T) Chemo Agents. The study population will include subjects ≥ 18 years of age with histologically/pathologically confirmed advanced or metastatic breast carcinoma. Subjects will have a medical history and physical assessment to include concomitant medication, standard of care breast cancer staging including mammogram, ultrasound, bone scan, chest x-ray or chest CT as well as blood tests for Complete Blood Count (CBC) with differentials, Complete Metabolic Panel (CMP). Prior to starting treatment, subjects will have a research blood draw and research

	biopsy. The study doctor will determine if the subject qualified to be enrolled in this study. Study treatment may continue as determined by the investigator until disease progression, intolerable AEs, death, voluntary withdrawal from the study by the patient, or discontinuation of the study by the sponsor. Treatment * Patients will receive Chloroquine 250mg daily together with Taxane or Taxane like chemo agents (Paclitaxel, Docetaxel, Abraxane, Ixabepilone) (C/T) Recommended prophylaxis for fluid retention/hypersensitivity reactions for Taxanes will be dexamethasone 8 mg Q12 hours for 3 doses starting the night prior to Taxanes or premedication per institution standards. *** See section 2.2.3 for full drug use and premedications.**
Inclusion Criteria:	1. Females with pathologically determined advanced or metastatic breast cancer. 2. Advanced breast cancer patients must have progressed or have residual disease after treatment with regimen that included at least 2 cycles of an anthracycline containing regimen. 3. Metastatic breast cancer patients must have had at least 4 cycles of an anthracycline containing regimen. 4. Patients must have measurable disease by Response Evaluation Criteria in Solid Tumors. 5. ≥18 years of age. 6. At least one measurable disease site, defined as lesion of ≥ 1 cm 7. No known underlying ocular/retinal pathology. 8. No medically documented preexisting auditory damage. 9. No cardiac conduction disturbances or medication potentially causing them: 10. QTc interval prolongation with other medications that required discontinuation of the treatment 11. Medication that might cause QT-prolongation or Torsades de pointes tachycardia is not allowed. (See appendix E) 12. ECOG PS of 0, 1, or 2. 13. Laboratory values within the following ranges: • Hemoglobin ≥9.0gm/dL (≥1.5µmol/L); transfusions permitted. • Absolute neutrophil count ≥1500/mm3 (1.5 x 109/L) • Platelet count ≥100,000/mm3 (100 x 109/L) • Creatinine (Cr) <2 X the upper limit of normal (ULN), Cr clearance (CrCl) ≥30 by Cockcroft and Gault • Alanine aminotransferase and aspartate aminotransferase <2 X the ULN; if liver metastases are present then must be <5 X the ULN, Bilirubin <2 X the ULN, for patients receiving Ixabepilone Potassium and Magnesium must be within normal limits. 14. Negative serum pregnancy test at the time of first dose for women of childbearing potential (WOCBP). For WOCBP, adequate contraception must be used throughout the study. For this study, acceptable methods of contraception include a reliable intrauterine device or a spermicide in combination with a barrier method. Women who are already on hormonal forms of birth control may continue that treatment but must also use a barrier method. 15. Ability to understand the requirements of the study, provide written informed

	consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments. 16. Patient must be willing to undergo breast biopsies as required by the study protocol.
Exclusion Criteria:	1. Radiation therapy within 2 weeks; or chemotherapy or non-cytotoxic investigational agents within 2 weeks of initiating study treatment. 2. Evidence of New York Heart Association class III or greater cardiac disease. 3. History of myocardial infarction, stroke, ventricular arrhythmia, or symptomatic conduction abnormality within 12 months. 4. History of congenital QT prolongation. 5. QT >500. 6. Concurrent severe or uncontrolled medical disease (i.e., active systemic infection, diabetes, hypertension, coronary artery disease, congestive heart Failure or major surgery) that, in the opinion of the Investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study. 7. Symptomatic central nervous system metastases. 8. The patient must be stable after radiotherapy for ≥2 weeks and off corticosteroids for ≥1 week. 9. Pregnant or nursing women. 10. Hypersensitivity or intolerance to Quinolones, Chloroquine, Paclitaxel, Docetaxel, Abraxane, Ixabepilone or other Taxane like drugs. 11. Active diagnosis of psoriasis or currently receiving treatment for psoriasis. 12. Alcoholism or hepatic disease. 13. History of epilepsy or seizures in the past 20 years. 14. Receiving concurrent treatment with prohibited medications (See appendix E) Examples include: ampicillin, antacids, cimetidine, cyclosporine, kaolin, magnesium trisilicate, coumarin-type anticoagulants, macrolide antibiotics (e.g., clarithromycin, isoniazid, and erythromycin), anti-HIV agents (e.g., ritonavir and delavirdine), antidepressants (e.g. fluoxetine and fluvoxamine), calcium channel blockers (e.g. verapamil and diltiazem), steroids and their modulators (e.g., gestodene, raloxifene, and mifepristone), and several herbal and dietary components (e.g. bergamottin and glabridin). 15. Severe renal insufficiency (CrCl <30mL/min [Cockcroft and Gault]). 16. History of gastrointestinal bleeding, ulceration, or perforation. 17. Concurrent use of potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, clarithromycin, atanazir, indinavir, nefazodone, neflinavir, ritonavir, saquinavir, telithromycin, and voriconazole. 18. Concurrent use of potent CYP3A4 inducers, such as dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbitol, and St. John's wort. 19. Used an investigational drug within 14 days preceding the first dose of study medication.
Statistical Design:	A sample size of 47 patients achieves 80% power to detect the difference between the null median overall response rate (ORR) of 30% and the alternative hypothesis median ORR 50% at a 0.05 significance level (alpha) using a two-sided binomial test.

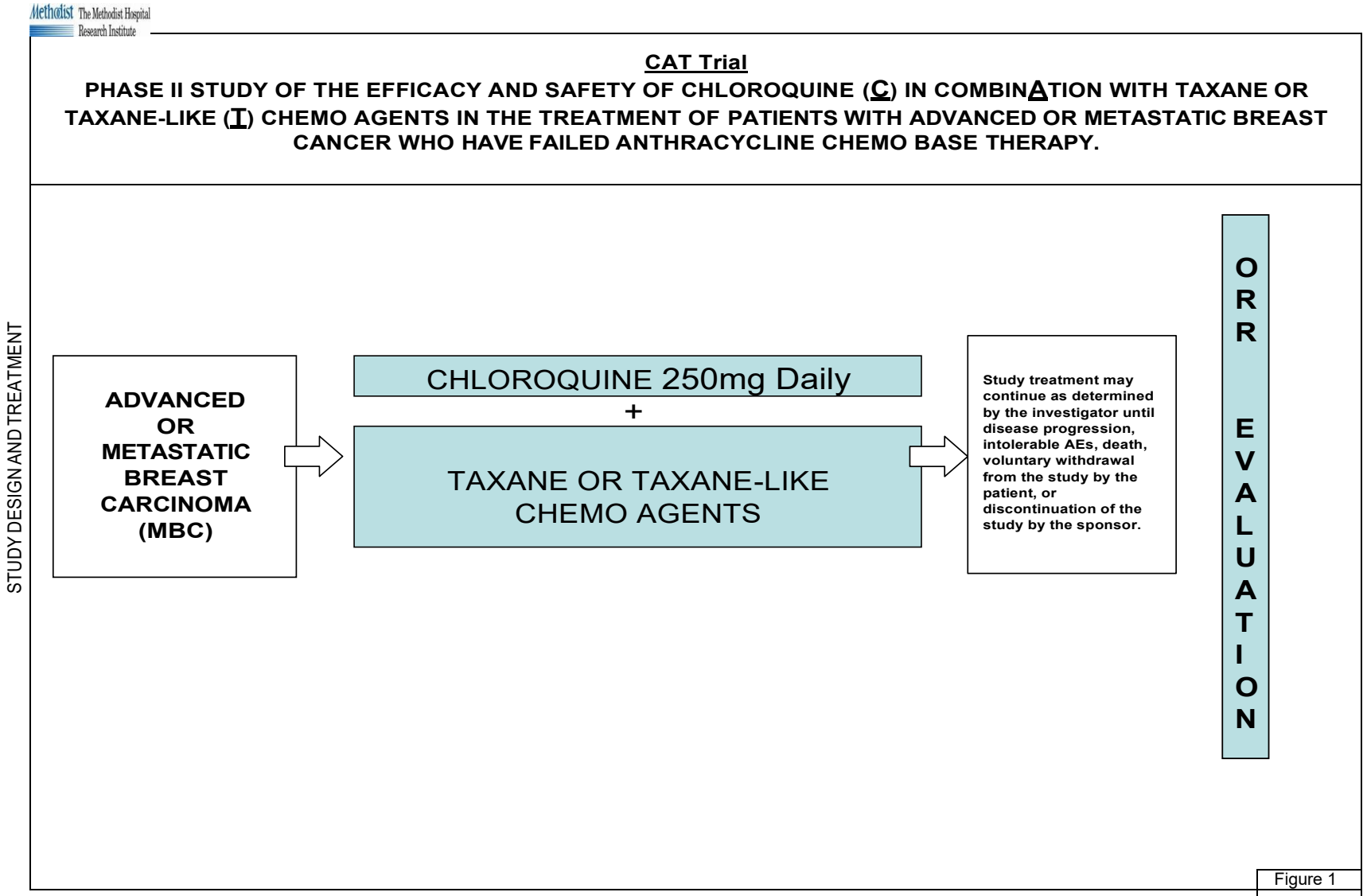

Methodist The Methodist Hospital Research Institute
CAT Trial
PHASE II STUDY OF THE EFFICACY AND SAFETY OF CHLOROQUINE (C) IN COMBINATION WITH TAXANE OR TAXANE-LIKE (T) CHEMO AGENTS IN THE TREATMENT OF PATIENTS WITH ADVANCED OR METASTATIC BREAST CANCER WHO HAVE FAILED ANTHRACYCLINE CHEMO BASE THERAPY.
STUDY DESIGN AND TREATMENT
ADVANCED OR METASTATIC BREAST CARCINOMA (MBC)
CHLOROQUINE 250mg Daily
+
TAXANE OR TAXANE-LIKE CHEMO AGENTS
Study treatment may continue as determined by the investigator until disease progression, intolerable AEs, death, voluntary withdrawal from the study by the patient, or discontinuation of the study by the sponsor.
ORR EVALUATION

Figure 1

Phase II Study of The Efficacy And Safety of Chloroquine (C) in CombinAtion With Taxane or Taxane-like (T) Chemo Agents in The Treatment of Patients With Advanced or Metastatic Breast Cancer Who Have Failed Anthracycline Chemo Base Therapy.

List of Tables

List of Figures

List of Appendices

1.0 Synopsis:

The tumor-initiating cell (TIC) or cancer stem cell hypothesis has fundamental clinical implications.[1-3] There is increasing evidence that human breast TICs are resistant to conventional treatment, including chemotherapy hormonal therapy, and radiation therapy. [4, 5] We have recently completed a neoadjuvant breast cancer trial, that provides strong clinical evidence for the resistance of breast TICs to conventional chemotherapy. [6] We demonstrated a three-fold increase in the proportion of TICs as marked by $CD44^{+}/CD24^{-/low}$ following chemotherapy in women with locally advanced breast cancer. Interestingly, in patients with HER2-amplified tumors, the EGFR/HER2 tyrosine kinase inhibitor lapatinib produced tumor shrinkage that was accompanied by a decrease in the proportion of TICs. [6] Our findings indicate that this subset of tumor cells, not affected by standard therapies, may be responsible for tumor initiation and self-renewal, thereby forming the basis of our hypothesis that these residual cells bearing stem cell-like properties may be responsible for treatment resistance, leading to relapse and metastases. From biopsies obtained from women with primary breast cancer, we have identified a "tumorigenic signature," Preliminary *in silico* mathematical analysis mapping Food and Drug Administration (FDA) approved drugs against these key regulatory pathways in our tumorigenic signature has yield several drug targets that may be re-purposed or re-positioned as therapies against TICs., and therefore may be effective treatment to prevent resistance and relapse. We have in vitro data that two of these drugs (chloroquine and auranofin) have activity in decreasing mammosphere formation efficiency (MSFE), an in vitro assay for self-renewal. [7-11] This is a phase II trial; 47 patients with diagnosis of advanced or metastatic breast cancer, who have failed anthracycline chemo base therapy, will be enrolled in the study. Patients will receive between 1) Chloroquine (C) together with Taxane or Taxane-like (Paclitaxel, Docetaxel, Abraxane, Ixabepilone) (T) Chemo Agents.

The study population will include subjects ≥ 18 years of age with histologically/pathologically confirmed advanced or metastatic breast carcinoma. Subjects will have a history and physical assessment to include concomitant medication, standard of care breast cancer staging including mammogram, ultrasound, bone scan, chest x-ray or chest CT as well as blood tests for Complete Blood Count (CBC) with differentials, Complete Metabolic Panel (CMP). Prior to starting treatment, subjects will have a research blood draw and research biopsy. The study doctor will determine if the subject qualified to be enrolled in this study. Study treatment may continue as determined by the investigator until disease progression, intolerable AEs, death, voluntary withdrawal from the study by the patient.

2.0 Introduction

Breast cancer is the most common cancer in women in the US with about 192,000 new cases in 2009. In 2010, an estimated 207,090 new cases of invasive breast cancer were expected to be diagnosed in women in the U.S., along with 54,010 new cases of non-invasive (in situ) breast cancer. Despite all of the significant advances in breast cancer biology, there has been limited progress in the treatment of advanced breast cancer, with little change in the overall survival for women with metastatic breast cancer over the last several decades.

3.0 Background and Rationale

3.0.1 Clinical Experience with Chloroquine

Our laboratories have developed robust preclinical models utilizing both *in vitro* systems such as the mammosphere (MS) culture and in vivo systems such as human breast cancer xenografts [6], allowing us to identify agents which selectively target TICs, as single agents or in combination. These models are critical since tumor initiating cells (TICs) comprise only a small percentage of

the tumor bulk, so that clinical tumor regression may not be observed with inhibitors that selectively target TIC self-renewal alone. Nonetheless, these agents in combination with conventional therapy may effectively kill both actively cycling or fully differentiated cells and the TIC subpopulation, leading to long term remission and eradication of cancer cells.
In addition, we have established a clinical trials network to conduct trials with selected TIC inhibitors, with a strong focus on correlative end-points. We propose to study the effects of combining repositioned or repurposed drugs with chemotherapy in women with metastatic breast cancers who are refractory to conventional chemotherapy. In our proposed clinical trial, we intend to begin with chloroquine in combination with taxanes in advanced breast cancer patients.

Preliminary Studies

Cancer stem cells are subpopulation in a total cancer cells with capacity of reconstructing the tumor from a single cell [15, 16] This has been a theory for two decades, and remains controversial. Regardless, cancer stem cells have been identified in numerous cancers including adrenal cancer, brain, ovary, leukemia, myeloma, breast, lung, and prostate cancers[6-8]. Importantly, pharmaceutical companies launched clinical studies specifically targeting cancer stem cells in recent years, as this subpopulation is closely correlated with cancer metastasis, drug resistance, and systemic recurrence. In breast cancer, the cancer stem cells have been characterized by the expression CD44, CD24, and aldehyde dehydrogenase [12, 19] In our laboratory, we identified these cells not only in in-vitro conditions but also in clinical cancer biopsies obtained from patients. We utilized mammosphere assay to enrich the cancer stem cells and identified cancer stem cell specific gene expression (Figure 2) and signaling pathways (Figure 3). Moreover, through bioinformatic drug screening of available drug databases, we identified chloroquine as a putative re-positioned drug targeting cancer stem cells.

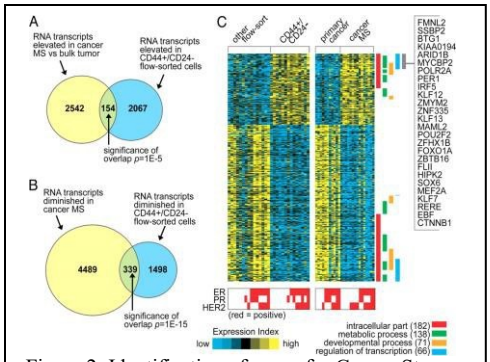


Figure 2. Identification of genes for Cancer Stem Cells

Chloroquine (CQ) is an anti-malaria drug used for 50 years and used widely to treat other diseases such as rheumatoid arthritis and lupus erythematosus. Intriguingly, in an attempt to control malaria in a county in Tanzania, CQ was administered for 5 years, and during this time the incidence of a hematologic cancer, Burkitt lymphoma which is endemic in that region, declined by 75%[20, 21] The tumor incidence returned to the old baseline 2 years after

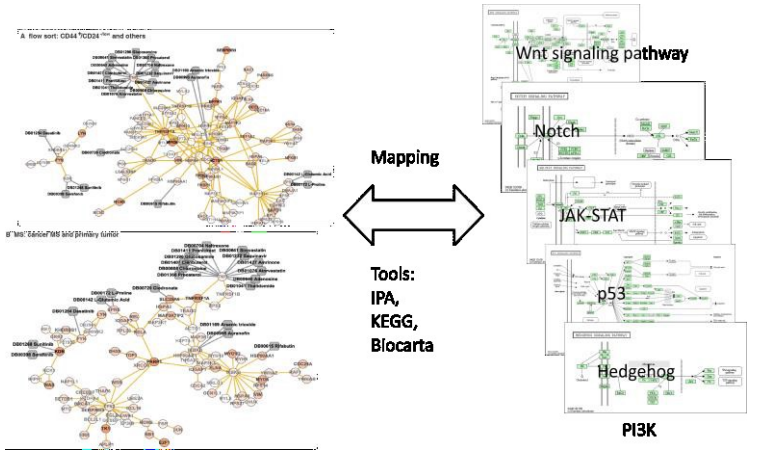


Figure 3. Gene Networks and Signaling Pathways up-regulated in Cancer Stem Cells

completion of the CQ trial. Recently, chloroquine has been been tested as an anti-cancer treatment in glioblastoma multiforme, a lethal form of brain cancer, and in earlier stages of in situ breast cancer. Even though the mechanism is not well understood, most of reports suggest that it works through inhibition of autophagy (self-eating survival mechanism) under p53-dependent pathway [22]. However, our preliminary data suggest chloroquine may function independent of p53, and further evaluation of this mechanism may have significant impact on selection of appropriate therapy. We expect that chloroquine will enhance cancer cytotoxic effects of conventional chemotherapies by inducing cell death within the cancer stem cells and thus, may decrease the cancer recurrence and death. More importantly, the long history of chloroquine use makes combination with chemotherapy a safe approach in carefully designed clinical trials.

Autophagy in normal cells can suppress tumorigenesis by removing toxic materials in the cell through p62 protein [23]. However, in the cancer cells, autophagy works as a survival mechanism by providing the cancer cell to cope with detachment stress (related with metastasis), frequent DNA damage, metabolic and oxidative stress, and chemotherapeutics [23]. Moreover, overexpression of LC-3 (a gene involved in autophagy) is frequently observed in more advanced cancers [23]. In addition to ensuring "survival" of cancer cells, autophagy is critical in carcinogenesis through its tumor microenvironment. Autophagy in cancer associated mesenchymal stem cells or fibroblasts supports the cancer stem cell survival through provision of nutrients or growth factors and triggers cancer metastasis [23-25].

Chloroquine induces p53-independent cell death accompanying incomplete autophagy and DNA damage. Previously, through bioinformatic analysis, we identified gene signatures specific for tumor initiating cancer stem cells (Figure 1 and 2) and screened several drug candidates (Figure 4) for a drug-reposition. We performed drug repositioning of FDA-approved drugs for any medical indication, as potential targets against cancer, in particular cancer stem cells. We discovered that chloroquine was the most effective in inhibiting mammosphere formation (Figure 5). In addition, we observed CQ induced apoptosis correlated with accumulation of autophagosome, DNA damage by western blot assay (Figure 6). The concentration of cytotoxic effect of CQ was seen as low as 1μM, 30-50 times lower than the reported concentrations.

Drugbank ID	Targets
DB00398 Sorafenib	KDR
DB01268 Sunitinib	KDR
DB00608 Chloroquine	TNF
DB00641 Simvastatin	TNF
DB01076 Atorvastatin	TNF
DB00615 Rifabutin	HSP90AA1
DB00720 Clodronate	SLC25A6
DB00995 Auranofin	IKBKB
DB01169 Arsenic trioxide	IKBKB
DB01254 Dasatinib	FYN

Figure 4. Screened Drug Candidates

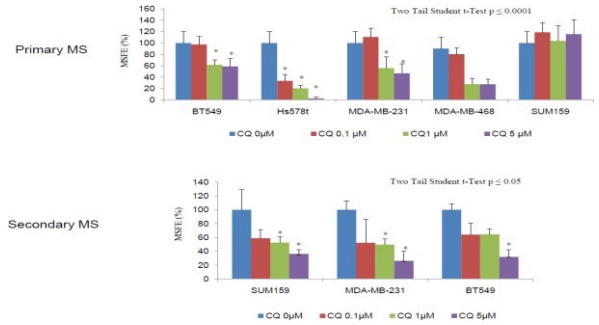


Figure 5. Chloroquine inhibits the mammosphere formation of TNBC cell lines

Interestingly, in the contrary to the previously reported results in the literature, our study showed that CQ induced DNA damage, and that these effects of CQ were p53-independent because the five TNBC cell lines examined had p53 gene mutations or deletions. Therefore, we hypothesize that the effects of CQ may in part involve

other members of the p53 family, like p63 and p73. Various publications that suggested that p73 can induce DNA damage [26, 27] while p63 is correlated in cancer metastasis and drug resistance[28] Also, p63 has been implicated in stem cell survival and differentiation [29, 30] Supporting this, breast cancer cells have been identified to express isoforms of p63 or p73[31, 32] However, their biological functions are not well described. Both N-terminal deleted isoforms lack DNA binding motifs and acts as a negative regulator of DNA binding isoforms of p63 or p73 [33, 36]

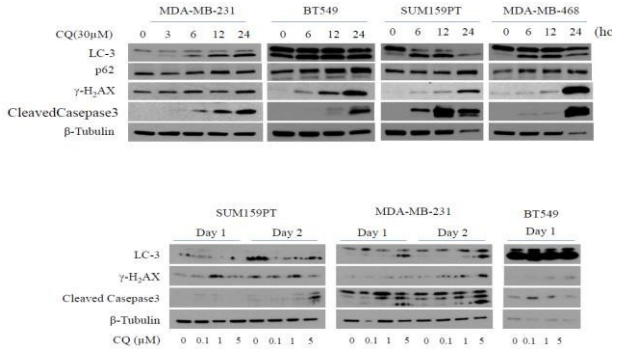


Figure 6. Chloroquine triggers autophagosome accumulation, DNA damage, and apoptosis in TNBC cell lines

Chloroquine induces apoptosis within the CD44high/CD24 neg cancer stem cell population in TNBC cell lines.

First, we compared how CQ will enhance a nano-micelle formulated conventional paclitaxel (mPTX). As seen in Figure 7, the combination treatment enhances the activation of caspase 3 and cleavage LC3. Interestingly, we observed the substantially decreased pStat3 after combination treatment which is important to maintain breast cancer stem cells. This is an imperative finding suggesting we can target cancer stem cells using CQ. Supporting this notion, we observed decrease in the viable cancer stem cells after CQ alone or the combination treatment through flow cytometric analysis (Figure 8). While we first confirmed the enhanced cytotoxic effects of mPTX by CQ on TNBC cell line (SUM159), further analysis of the results led us to the direct evidence that CQ have the ability to control the viability of cancer stem cells (Figure 8 and 9). Similar results were observed with a different TNBC cell line MDA-MB-231, well characterized for its metastatic propensity and chemoresistance (Figure 9). Here, CQ reduced dramatically the cancer stem cell enriched populations by 30 % in CD44high /CD24neg, or 80% in

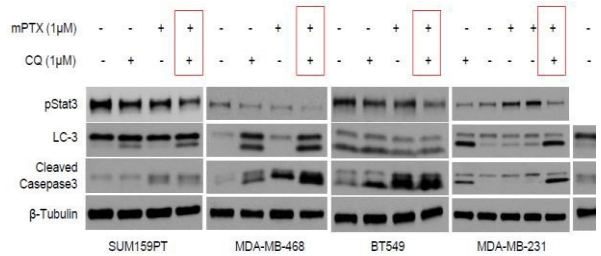


Figure 7. Combination treatment of chloroquine and mPTX enhanced cell death in comparison to the single treatment of each.

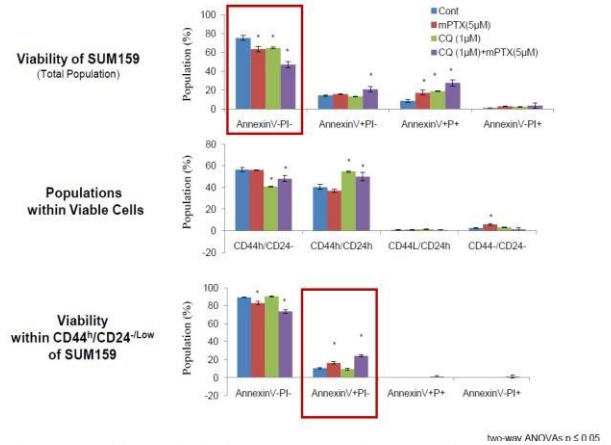


Figure 8. Chloroquin induce apoptosis in CD44h/CD24- stem cell population. AnnexinV-/PI- : Viable cells. AnnexinV+ or PI+ : apoptotic or dead cells.

ALDH1 positive subpopulations. Thus, we hypothesize that CQ can reduce the cancer stem cells in cell lines by p53 independent mechanisms, perhaps by involving other members of the p53 family.

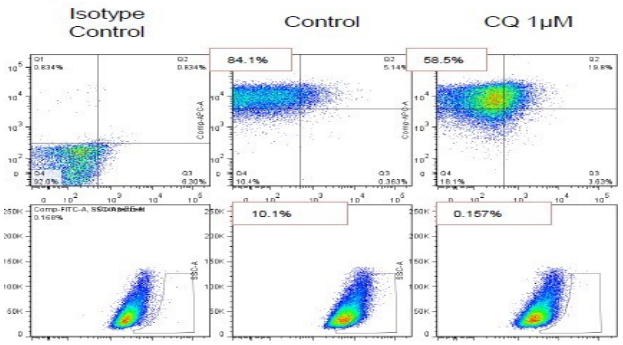


Figure 9. Chloroquine reduced the cancer stem cell poluation within MDA-MB-231 TNBC cell line.

The pathways of cytotoxic effect of chloroquine differ by p53 status in Breast Cancers.

Because of the promising effects of CQ on cancer stem cells, we investigated the mechanism of action of CQ, focusing on autophagy and the cell death-related pathways, PI3K-mTOR and p73 expression in SUM159 and MDA-MB-231 cells. SUM159 cells lack p53 while MDA-MB-231 cells express both wild type and mutant p53. Despite of the similar results in reducing cancer stem cell populations and pStat3 in combination treatment with mPTX, contrary to our expectations, the signaling propagation was very different in both cell lines. In SUM159 cells, the PI3K-mTOR pathways were unaffected, as confirmed by p-mTORs and pAkt expression. The rapamycin sensitive mTOR complex protein, Raptor expression increased with increasing doses of chloroquine (Figure 10). The level of pStat3 showed no change with CQ alone. However, in MDA-MB-231 cells, the mTOR pathway was severely affected by CQ and the rapamycin insensitive mTOR complex protein, Rictor decreased as the dose of CQ increased. This dramatic change was then followed by rapid reduction of pStat3. In addition, we also observed contradicting regulation of p73 expression by CQ. In SUM159 cells, the expression p73 isoforms decreased after CQ treatment while p73α expression increased in MDA-MB-231 cells. In addition, the dominant negative regulator of p73, the expression of ΔNp73α decreased as CQ dose increased in SUM159 but not in MDA-MB-231. Despite the differences in mechanism, autophagy was

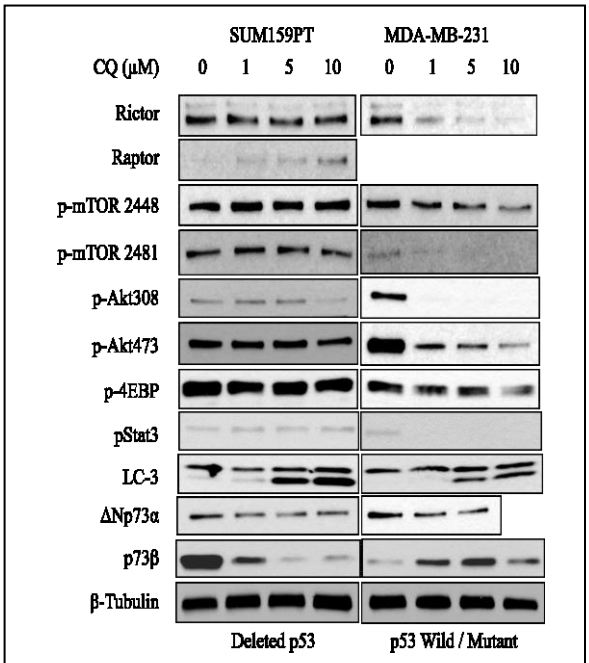


Figure 10. Chloroquine follows different signaling routs to cell death depending on p53 genetic status in TNBC.

induced in both cells lines, and we confirmed increased LC-3 cleavage in both cell lines as the dose of CQ was increased.

3.0.2 Summary of Experience with Chloroquine.

Chloroquine has been extensively used as an antimalarial for many decades. It is safe, well tolerated, and with very few side effects. More recently, it has been studied in cancer patients, mainly as an agent that affects survival pathways like autophagy.

Briceno et al. evaluated the addition of chloroquine to conventional chemotherapy and surgery for those patients with Glioblastoma Multiforme (GBM), 41 patients with GBM received chloroquine as an optional adjuvant administered concurrently with conventional chemotherapy, and compared with patients with GBM who did not receive chloroquine were included in this analysis as control subjects. The end point observed was time of survival after surgery. They found the survival time in patients treated with chloroquine as 25 ± 3.4 months, as compared with the 11.4 ± 1.3 months in control subjects (P = .000; OR = 0.4; 95% CI = 0.26-0.6); the difference remained significant after regression analysis for possible clinical confounders. In agreement with this report, chloroquine exerts a strong adjuvant effect when added to the conventional treatment of GBM. In this large cohort of unselected patients with GBM who were treated with chloroquine, the median survival time doubled as compared with that of control subjects. [37] More important, chloroquine when administrated with a variety of chemotherapeutic agents did not increase adverse events, and thus can be safely given with taxanes in patients with advanced breast cancer who have limited prognosis.

The American Academy of Ophthalmology recommendations for screening of chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy were published in 2002, but improved screening tools and new knowledge about the prevalence of toxicity have appeared in the ensuing years. New data have shown that the risk of toxicity increases sharply toward 1% after 5 to 7 years of use, or a cumulative dose of 1000 g, of HCQ or 460g of CQ. The risk increases further with continued use of the drug. The prior recommendation emphasized dosing by weight. However, most patients are routinely given 400 mg of HCQ daily (or 250 mg CQ). This dose is now considered acceptable, except for individuals of short stature, for whom the dose should be determined on the basis of ideal body weight to avoid overdosage. A baseline examination is advised for patients starting these drugs to serve as a reference point and to rule out maculopathy, which might be a contraindication to their use. Annual screening should begin after 5 years (or sooner if there are unusual risk factors). Newer objective tests, such as multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF), can be more sensitive than visual fields. Fundus examinations are advised for documentation, but visible bull's-eye maculopathy is a late change, and the goal of screening is to recognize toxicity at an earlier stage. [38]

3.0.3 Cytokine Background and Rationale.

The measurement of soluble cytokines in serum and plasma is becoming increasingly important in the study and management of many diseases. As a result, there is a growing demand for rapid, precise, and cost-effective measurement of such analytes in both clinical and research laboratories. Multiplex bead array assays (MBAA) provide quantitative measurement of large numbers of analytes using an automated 96-well plate format. Wide assortments of tests have been devised for MBAA using both immunological and molecular ligands. The potential advantages of these assays are apparent, such as the ability to independently and quantitatively assay multiple analytes simultaneously in small volumes of material and the collection of data from numerous beads for each ligand to provide statistical rigor. The potential cost- and time-

savings that could be accrued by use of MBAA in comparison to other methods provides a strong impetus for the routine use of these in both the research and clinical laboratories. This new technology allows for (1) evaluation of multiple analytes in a single sample; (2) utilization of minimal sample volumes to glean data; (3) reproducibility and results comparative with previous experiments; (4) direct comparison with existing assays; and (5) a more rapid evaluation of multiple samples in a single platform. The cytometric bead array (CBA) system enables simultaneous measurement of multiple analytes in sample volumes too small for traditional immunoassays.[39-46]

4.0 OBJECTIVES

4.1 The primary objective:
To determine the anti-tumor activity of the combination of Chloroquine + Taxane or Taxane-like chemo agents (Paclitaxel, Docetaxel, Abraxane, Ixabepilone) (C/T) measured by overall Response Rate (ORR).

4.2 The secondary objective(s):
• To assess the safety and tolerability of the combination of C/T.
• To assess the response rate and tumor control rate (TCR) of patients receiving C/T.
• To assess the Time to Progression (TTP) of patients receiving C/T.
• To assess the duration of response (DOR) of patients receiving C/T.

4.3 Exploratory Objective(s):
• To evaluate biomarkers for response and toxicity of the combination of C/T.
In patients with accessible tumor, biopsies will be conducted at baseline, prior to the second cycle of treatment, and at the end of the treatment. If the patient progresses while in treatment a new biopsy will be taken before the patient start the new treatment. (Please see section 5.3.3)

5.0 Study Flow chart or Schedule of Events

Procedure	Screening/Baseline Visit	Prior to Each Cycle	End-of- Treatment Visit [a]	End of Study Assessments/ Follow-up [q]
Eligibility Assessments				
Obtain Informed Consent	X			
Confirm Inclusion/Exclusion Criteria Met [b]	X			
Obtain Medical History	X			
Safety Assessments				
Physical Exam	X	X	X	X
ECOG performance scale [b]	X	X	X	X
Record Weight, Height and Vital Signs	X	X	X	X
Eye Exam[r]	X			
Assess Signs and Symptoms and Adverse Events [c]	X	X	X	X
Perform Pregnancy Test in WOCBP [d]	X			
Perform mammogram [e] *	X		X	
Perform ultrasound of breast and nodal region [e] *	X		X	
Perform CT scan Chest and Abdomen or CXR [f]	X			
Perform Bone scan	X			
Perform Laboratory Tests [gh]	X	X	X	
Biopsies [i]**	X	**	X	
Whole Blood/ serum [j] ***	X	***	X	
Perform Electrocardiogram [k]	X			
Perform 2D Echocardiogram or MUGA	X			
Efficacy Assessments				
Evaluate Tumor Response RECIST Criteria [m]	X		X	
Clinical Drug Supplies				
Chloroquine administration [n]		X		
Infusion visit[p] / Premed Before Infusion [o]		X		

Table 1

a. Evaluate subjects who discontinue the protocol for reasons other than disease progression (AEs) every 4 weeks until progression or until they receive additional anti-cancer therapy.

b. ECOG Performance Status of 0-1and 2 is required for study entry. ECOG performance status will be recorded at baseline, prior to each cycle, at the end of treatment and at the end of the study assessment.

c. Document signs and symptoms and adverse events at least every 4 weeks until all study drug-related toxicities resolve, stabilize, return to baseline, or are deemed irreversible. Adverse events will be collected at baseline with the medical history and will be recorded as an adverse event only if they increase in severity or toxicity.

d. Pregnancy tests (serum or urine) should be performed within 72 hours of study start, or whenever pregnancy is suspected.

e. Unilateral mammogram and ultrasound should have been performed any time within 4 weeks prior to beginning of the study treatment in patients with locally advanced cancer who have failed anthracycline chemotherapy. *MRI (magnetic resonance imaging) should be performed only if requested by the physician.

f. Perform Bone Scan, CT scans chest& abdomen as an initial workup Patients with metastatic disease must repeat tests every eight weeks (+/- 2 weeks) or as a clinically indicated. Repeat testing for patients with advanced breast cancer is at the discretion of the investigator. A Chest XRay (PA & Lateral) can be substituted for a CT scan for patients with advanced breast cancer.

g. Comprehensive Metabolic Panel to include sodium, , chloride, calcium, glucose, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, and albumin. Complete blood count must include Hemoglobin, Hematocrit, RBC, WBC, Platelets with differential Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils. CrCL “CrCl = [(140 - age) x IBW] / (Scr x 72) (x 0.85 for females)” before every cycle for patients with an abnormal creatinine. Potassium and Magnesium must be collected at baseline and prior to each infusion on patients receiving Ixabepilone.

h. Perform laboratory tests within 72 hours of beginning each cycle. Perform baseline laboratory tests within four (4) weeks before administration of study drug.

i. Biopsies will be obtained from accessible sites at baseline, **prior to the second cycle of chemotherapy and at completion of study.

j. Whole blood/serum collection for cytokine arrays, ***prior to the second cycle of chemotherapy and at completion of study.

k. A 12-lead EKG at baseline; QRS measurement is required. Electrocardiogram (EKG) with QRS measurement will be repeated whenever clinically indicated.

m. Evaluate tumor response using RECIST criteria before chemotherapy and every 8 weeks (+/- 2 weeks) from Day 1 to disease progression.

n. Subjects who are to receive Chloroquine will receive 250mg po daily. **Chloroquine will be self-administered daily with water within 30 minutes after a meal**. The site must perform all appropriate drug accountability.

o. Subjects will be premedicated approximately 1 hour before a taxane or taxane-like infusion (see section 2.2.3 for doses and premedication). Standard anti-emetics for moderately emetogenic regimen, together with standard premedication will be prescribed with chemotherapy. Recommended prophylaxis for fluid retention/hypersensitivity reactions for taxane or taxane-like chemotherapy will be dexamethasone 8 mg Q12 hours for 3 doses starting the night prior to the infusion or premedication per institution standards.

p. Monitor the subject for hypersensitivity reactions during and after all infusions.

q. End of study visit will occur due to disease progression, as determined by the investigator until intolerable AEs, death, voluntary withdrawal from the study by the patient, or discontinuation of the study by the sponsor. Vital signs including blood pressure, heart rate and temperature will be performed during this visit. Toxicity assessment will be continuous throughout the study. CTC Version 4.0 will be used to grade toxicities (See Appendix C).

r. A baseline ophthalmologic examination will be used as a reference point and to rule out maculopathy, Baseline exam for patient with no significant medical history can have a baseline exam within one year of starting treatment. Patients with a history of diabetes, HTN, ocular abnormalities or any other significant medical history will have an eye exam within 30 days of starting treatment.

5.1 Study Procedures by Visit and Treatment Cycle

Laboratory analyses and clinical examinations are to be repeated for total treatment duration. Radiologic examinations are to be performed before chemotherapy every eight weeks or as clinically indicated. (From randomization to disease progression). Study treatment may continue as determined by the investigator until disease progression, intolerable AEs, death, voluntary withdrawal from the study by the patient, or discontinuation of the study by the sponsor. **The maximum number of treatment cycles allowed is 6.**

Treatment * Patients will receive Chloroquine 250mg daily together with Taxane or Taxane like chemo agents (Paclitaxel, Docetaxel, Abraxane, Ixabepilone) (C/T) Recommended prophylaxis for fluid retention/hypersensitivity reactions for taxanes will be dexamethasone 8 mg Q12 hours for 3 doses starting the night prior to taxanes or premedication per institution standards.

*** See section 2.2.3 for full drug use and premedications.**

5.2 Screening/Baseline visit

Informed consent must be obtained before performing any study-related procedures. Screening procedures may be done up to 4 weeks prior to the start the treatment for metastatic breast carcinoma.

The following will be obtained at screening, prior to beginning study medication:

-General history and physical exam, to include height, weight, blood pressure, heart rate, temperature, a clinical breast exam, and palpation of lymph nodes.

-General ophthalmologic exam at baseline, and during treatment if clinically indicated.

-Medical history should include relevant underlying conditions and concomitant medications.

-Baseline signs and symptoms are to be recorded and followed throughout the trial.

- Laboratory assessments (see below).
- Breast imaging in patients with advanced primary cancers who have failed anthracyclines (see below).
- Bone scan
- CT chest and abdomen
- EKG and 2D ECHO or MUGA

5.2.1 Radiological Evaluation Visit

Perform radiological workup as per institutional guidelines to determine baseline metastatic disease. This radiological evaluation should be completed within 6 weeks before study drug administration. If more than 6 weeks have elapsed since the baseline radiological evaluation, a second radiological workup must be repeated before the initial treatment with the study drug. If, at any time, progressive disease is suspected, a complete radiological evaluation must be performed. MRI (magnetic resonance imaging) should be performed only if requested by the physician.

Radiologic examinations are to be performed before chemotherapy every eight weeks or as clinically indicated. Use RECIST criteria to evaluate response. (See section 9.0)

5.2.2 Pre-Infusion Clinic Visits

The following assessments should be performed at each pre-infusion clinic visit. To allow for weekends, holidays, etc., study procedures may be completed within a ± 4 day window. Laboratory tests need to be completed within 72 hours of infusion.

-Physical exam with a clinical breast exam and ECOG status.

-Biopsies of accessible sites (mainly skin and breast) are to be performed at baseline, prior to the second cycle of chemotherapy, at the end of the study or prior to switching therapy.

-Laboratory assessments to include a CBC/differential and serum chemistry panel, as defined in Section 2.0.

-Record all concomitant medications added and/or changed.
-Assess compliance to study medications and infusion schedule.
-Non-serious and serious adverse events should be recorded and graded appropriately as discussed in Section 14.
-Dispense supply of the study drug chloroquine plus either one of the next list of drugs: (Paclitaxel, Taxotere, Abraxane, Ixabepilone) every 3 weeks.

5.2.3. Infusion Visits

Subjects eligible for treatment will receive treatments per NCCN guidelines:
A: Chloroquine 250mg po daily together with Paclitaxel 175 mg/m^2 three hours infusion every two or three weeks or Paclitaxel 80 mg/m^2 weekly. Or
B: Chloroquine 250mg po daily together with Taxotere 75 mg/m^2 (or 100mg/m^2 in advanced breast cancer patients) administered intravenously over one hour every three weeks. Or
C: Chloroquine 250mg po daily together with Abraxane 260 mg/m2 administered intravenously over 30 minutes every three weeks or 100mg/m^2 administered weekly. Or
D: Chloroquine 250mg po daily together with Ixabepilone is 40 mg/m^2 administered intravenously over three hours every three weeks. Doses for patients with body surface area (BSA) greater than 2.2 m^2 should be calculated based on 2.2 m^2.
Infusion times for chemotherapy are approximate and can vary slightly. Infusion time can be slowed for the safety of the patient.
Dose reductions are allowed at the discretion of the investigator for patient safety.

Subjects will be premedicated approximately 1 hour before the infusion. Standard anti-emetics for moderately emetogenic regimen, together with standard premedication will be prescribed with chemotherapy. Recommended prophylaxis for the taxane and taxane-like chemo agent includes:

- Paclitaxel premedication may consist of dexamethasone 20 mg po administered approximately 12 and 6 hours before Paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to Paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before Paclitaxel or use premedication per institutional standards.
- Docetaxel premedicated may consist of oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to Taxotere administration or use premedication per institutional standards.
- Abraxane, no premedication is needed.
- Ixabepilone premedication may consist of H1 antagonist (e.g., diphenhydramine 50 mg orally or equivalent) and a H2 antagonist (e.g., ranitidine 150 - 300 mg orally or equivalent). Or use premedication per institutional standards.

5.2.4. End-of-Treatment/Early Termination Visit

After confirmation of progression disease or one (1) week after the patient has withdrawn from the study for any reason other than “completed” treatment:

- Physical exam with a clinical breast exam and ECOG status.
- Biopsy is to be performed (prior to initiation of new therapy) if the patient has progressed, or at the end of six cycles. If the patient has locally advanced cancer, a surgical specimen will be obtained instead of a core biopsy after 4 – 6 cycles.
- Laboratory assessments to include a CBC/differential and serum chemistry panel, as defined in see Section 2.0. Record all concomitant medications added and/or changed.
- Assess compliance to study medications and infusion schedule.

- Non-serious and serious adverse events should be recorded and graded appropriately as discussed in section 14.
- Perform radiological evaluation to determine the tumor status using RECIST criteria (see Section 9.0).

5.2.5. End of Study Assessments/ Follow-up

End of study visit will occur when progression disease is confirmed. Vital signs including blood pressure, heart rate and temperature will be performed during this visit. Toxicity assessment will be continuous throughout the study. CTC Version 4.0 will be used to grade toxicities (See Appendix C web link).

Upon completion of the investigational therapeutic regimen, subjects will be followed for adverse events for a period of 30 days after the last dose of investigational product. Patients with abnormal laboratory or clinical findings that are believed to be treatment related will be followed until the condition resolves or stabilizes, or until the laboratory values are no longer considered clinically significant as judged by the investigator. New adverse events that occur during the 30 day follow-up period will only be recorded if the investigator believes there is a possibility that the adverse event is drug-related. Adverse events that are clearly not drug-related will not be recorded. Ophthalmologic evaluation at any time during the treatment only if clinically indicated. A follow-up for patients that have not progressed after 6 months of treatment completion is required.

5.3 Details of Procedure

Compliance

Compliance with Chloroquine will be evaluated by a physical pill count at the scheduled clinic visits. Subjects will be instructed to bring their used blisters of Chloroquine to each return visit, along with any unused tablets. The investigator/designee will count the number of remaining tablets at each visit to assess compliance. In the event that the subject forgets to bring their used study meds to their clinic visit, compliance will be assessed by direct questioning of the subject. In this case, subjects should be counseled to bring their used drug bottles to their next scheduled infusion appointment so that compliance may be confirmed by pill count. Subjects should be instructed to report any missed doses of Chloroquine to the study coordinator. Compliance with Chloroquine will be calculated by the ratio of number of pills actually taken to the number of pills that should have been taken. Compliance will be defined as a ratio ≥ 0.75. Subjects with ratios between 1.00 and 0.75 will be allowed to continue on study. Study staff should ensure subject understanding of dosing instructions for subjects whose compliance is less than 100%. In addition, the importance of compliance with anticancer therapy should be reinforced. Subjects found to be in less than 75% compliance on more than one occasion will be taken off study for non-compliance. Patients who fail to keep more than 75% of their scheduled standard of care (SOC) infusions will be taken off study for non-compliance.

5.3.1 Safety Assessments

All participants will be assessed by a physician for pre-existing medical conditions and baseline physical abnormalities prior to the initiation of investigational therapy. Patients presenting with any medical history, physical exam, or laboratory abnormality that, in the opinion of the treating physician, would put the subject's safety at risk will be excluded. Baseline signs and symptoms are to be recorded and followed throughout the trial. These will be monitored throughout the study and recorded if they increase in severity or frequency during treatment or within the follow up period. Participants will be assessed for adverse events by a physician or designated midlevel provider prior to each chemotherapy infusion while the patient is on study. Vital signs including blood pressure, heart rate and temperature should be performed at each physical exam. Assessments may be performed more frequently if clinically indicated. In addition,

hematology and serum chemistry profiles will be drawn prior to the initiation of treatment and prior to every infusion to determine whether the study drug combination affects hematologic values, electrolytes or liver function tests. Laboratory assessments will be performed more frequently if clinically indicated. This clinical and laboratory data will be used to determine whether these women taking Chloroquine have any symptoms or side effects associated with the study medication. Subjects will be followed for adverse events for a period of 30 days after the completion of investigational therapy. Patients with abnormal laboratory or clinical findings that are believed to be treatment related will be followed every four weeks until the condition resolves or stabilizes, or until the laboratory values are no longer considered clinically significant. CTC Version 4.0 will be used to grade toxicities.
Laboratory tests may be done more frequently if medically indicated. If CTC Grade 4 hematologic toxicity is seen; CBC + differential + platelets should be repeated every 3 - 4 days until recovery.
Patients who are on chloroquine for more than 24 weeks will be referred to the Ophthalmology service for retinal examination. Patients may require electroretinogram (ERG), as recommended by the ophthalmologist. The cost of the ERG will be paid for by the study.

5.3.2 Efficacy Assessments

A clinical assessment as well the radiological work up will be performed to assess disease status at baseline. Clinical tumor and metastatic site response will be assessed every eight weeks for patients with metastatic disease. Disease progression suspected from clinical tumor response assessments during any cycle should be confirmed by radiological work-up that would include bone scan, CT scan of chest and abdomen. If progression disease is confirmed a biopsy will be take prior to any treatment. An electrocardiogram (EKG) will be performed prior to the initiation of investigational therapy in order to ensure that the subject has adequate cardiac function; QRS measurement is required. The electrocardiogram (EKG) with QRS measurement will be repeated whenever clinically indicated.

5.3.3 Tissue Specimen Acquisition

Biopsies will be obtained from patients at baseline prior to the second cycle of chemotherapy, and at the end of treatment. If the patient progresses while in treatment a new biopsy will be taken before the patient start the new treatment. In order to maximize the likelihood of obtaining sufficient tissue, approximately four to six biopsies using a Bard Vacora Biopsy Instrument (or equipment that provides a sample of comparable quality) are taken. Biopsies are performed under local anesthesia, using the same entry point but reorienting the needle. The biopsies are done in the clinic or doctor's office by the participating oncologist or surgeon. The investigators in this unit have considerable experience with this technique. The outside needle is 14-gauge (2.1 mm), with a smaller inside cutting needle to obtain the biopsy. The length of the needle penetration is 22 mm and the length of the needle is 10 cm. Multiple biopsies of approximately 2mm x 10-20mm will be obtained from each time point. Potential complications from core biopsies include bleeding, pain or infection. We have conducted several neoadjuvant studies over the past decade, involving several thousand biopsies, and the complications to date have been few and mild. A portion of the core biopsies will be snap frozen on dry ice and stored at -80^0C for cDNA array analysis. The remaining specimens will be fixed in formalin for immunohistochemical analysis.
<u>cDNA expression arrays on biopsies</u> Half of the biopsy specimens will be immediately snap-frozen at -80^0C for cDNA array analysis. The remaining specimens will be fixed in formalin for diagnostic and immunohistochemical analysis. As human breast cancers consist of many different cell types, including not just carcinoma cells but also additional epithelial cell types, stromal cells, and adipose cells, we will ascertain the tumor cellularity of the core biopsies for

epithelial cores by hematoxylin-eosin (H&E) and pan-cytokeratin stains before analysis (Fig. 11).

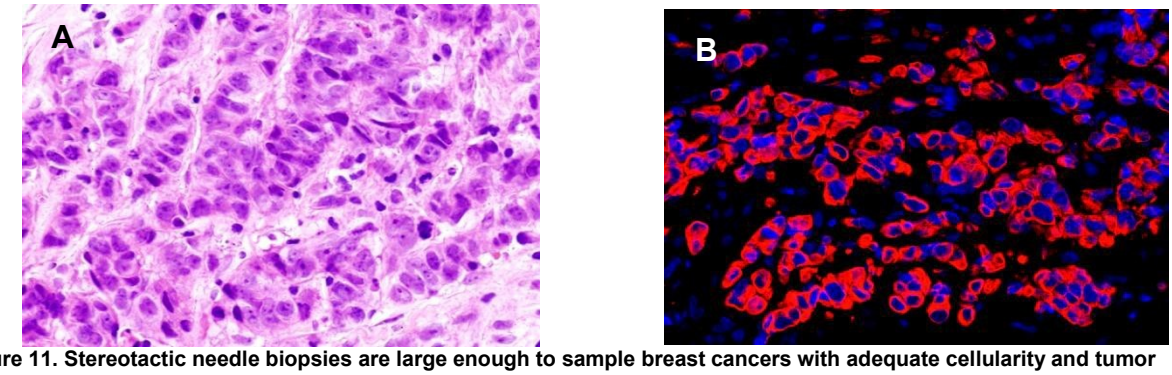


Figure 11. Stereotactic needle biopsies are large enough to sample breast cancers with adequate cellularity and tumor cells. This example shows a core fragment containing tumor cellularity of 75% on H&E (Fig. 11A), and on pan-cytokeratin marker (Fig. 4B).

RNA isolation, cDNA synthesis, and combined in vitro transcription and biotin labeling (IVT) on the frozen samples will be carried out according to protocols recommended by Affymetrix GeneChip™ (Santa Clara, CA). Briefly, total RNA is isolated, and double-stranded cDNA is synthesized from total RNA using a chimeric oligo-dT/T7 RNA polymerase. Core biopsies typically yield 3-6 micrograms of total RNA. The IVT products will then be passed over a mini-RNA isolation column, and the cRNA target population will be chemically fragmented to 100-200 bases. The fragmented cRNAs (~20 µg) will then be hybridized to the Affymetrix HG-U1332 GeneChips™, which contain ~30,000 gene probes. The microarrays were pre-hybridized, hybridized, washed, and stained with streptavidin-phycoerythrin.

Timing of biopsies

Study patients will be consented for core biopsies at baseline prior to the second cycle of chemotherapy and at the end of treatment. If the patient progresses while in treatment a new biopsy will be taken before the patient start the new treatment. If the patient has locally advanced cancer, a surgical specimen will be obtained instead of a core biopsy

Pre-treatment / Baseline: Tumor biopsy specimens will be obtained prior to initiating therapy. A baseline research biopsy will be performed in accessible sites, like breast, skin, soft tissue and nodes. Four to six biopsies will be obtained for gene expression , immunohistochemistry, stem cell and other analyses.

Before Cycle 2: Core biopsies will be obtained before cycle 2 of treatment, in accessible sites, as above.

End of treatment: Core biopsies will be obtained at end of treatment, in accessible sites, as above. A surgical specimen may be obtained in lieu of a biopsy in patients who undergo surgery.

Cytokine arrays

Blood specimens will be collected for multi-analyte analysis with Luminex xMAP Technology. Luminex xMAP technology allows for the detection of multiple analytes simultaneously in a single assay. Luminex offer the broadest selection of analytes across a wide range of disease states, including inflammation, cancer and more.

Timing of blood:

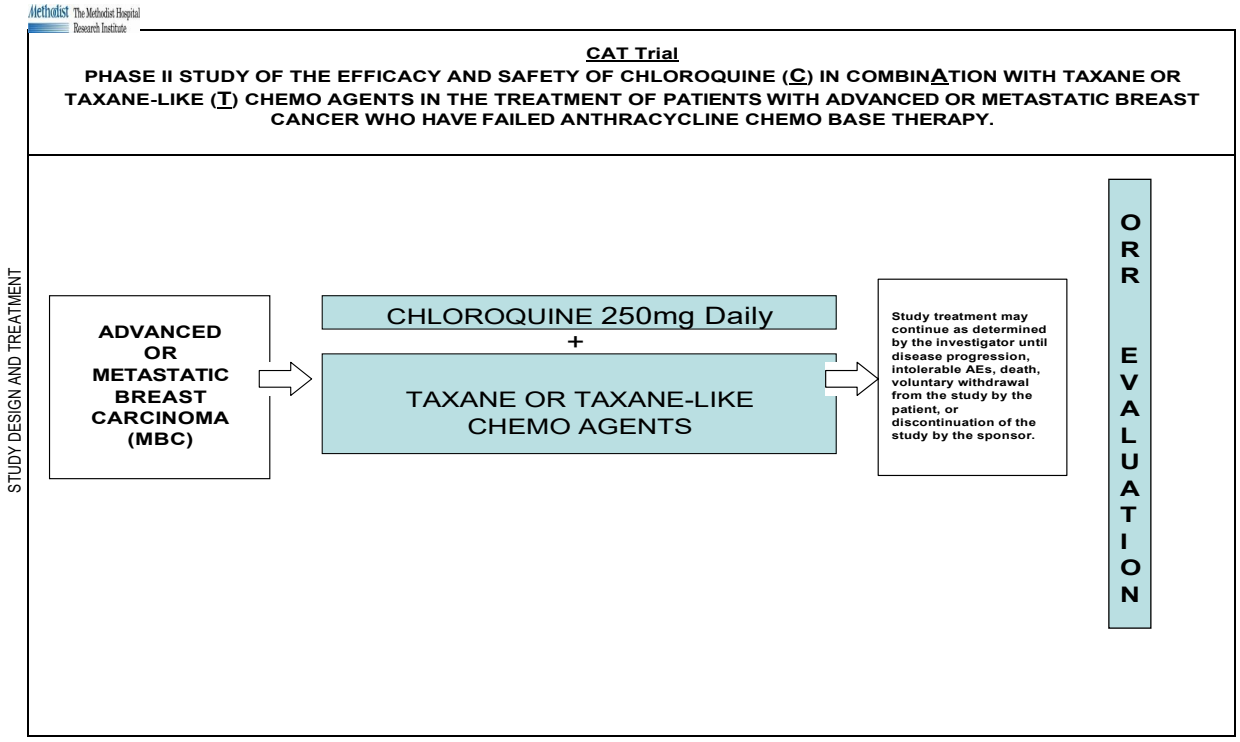
Whole blood/serum collection for cytokine arrays at baseline, prior to the second cycle of chemotherapy, and at completion of study or if the patient progress while on treatment a blood draw will be done before the patient start the new treatment. One venous blood sample of 10 mLs will be collected.

6.0 TIMELINE and MILESTONES

Specific Aims	Year 1	Year 2	Year 3
Specific Aim 1: To determine the anti-tumor activity of the combination of Chloroquine + Taxane or Taxane-like chemo agents (Paclitaxel, Docetaxel, Abraxane, Ixabepilone) (C/T) measured by overall Response Rate (ORR).			
a. Planning and protocol writing	--→		
b. Clinical recruitment	----------→		
c. Overall Response Rate Analysis	--------→		
Specific Aim 2: To Assess Safety, Tolerability and Responses Rates.			
a. Safety and Tolerability of the Combination	----------→		
b. Response rate and tumor control rate	--------→		
c. Time to Progression (TTP)	--------→		
d. Duration of response (DOR)	--------→		
Specific Aim 3: Biomarkers Evaluation			
a. To evaluate biomarkers for response and toxicity of the chloroquine in combination with taxane or taxane-like chemo agents	----------→		

Table 2

7.0 Study Design



8.0 Study Population

The study population will include subjects ≥ 18 years of age with histologically confirmed metastatic breast carcinoma.

8.1 Inclusion Criteria:

11. Females with pathologically determined advanced or metastatic breast cancer.
12. Advanced breast cancer patients must have progressed or have residual disease after treatment with regimen that included at least 2 cycles of an anthracycline containing regimen.
13. Metastatic breast cancer patients must have had at least 4 cycles of an anthracycline containing regimen.
14. Patients must have measurable disease by Response Evaluation Criteria in Solid Tumors.
15. ≥18 years of age.
16. At least one measurable disease site, defined as lesion of ≥ 1 cm
17. No known underlying ocular/retinal pathology.
18. No medically documented preexisting auditory damage.
19. No cardiac conduction disturbances or medication potentially causing them:
20. QTc interval prolongation with other medications that required discontinuation of the treatment

11. Medication that might cause QT-prolongation or Torsades de pointes tachycardia is not allowed. (See appendix E)
12. ECOG PS of 0, 1, or 2.

13. Laboratory values within the following ranges:
    - Hemoglobin ≥9.0gm/dL (≥1.5µmol/L); transfusions permitted.
    - Absolute neutrophil count ≥1500/mm3 (1.5 x 109/L)
    - Platelet count ≥100,000/mm3 (100 x 109/L)
    - Creatinine (Cr) <2 X the upper limit of normal (ULN), Cr clearance (CrCl) ≥30 by Cockcroft and Gault
    - Alanine aminotransferase and aspartate aminotransferase <2 X the ULN; if liver metastases are present then must be <5 X the ULN, Bilirubin <2 X the ULN, for patients receiving Ixabepilone Potassium and Magnesium must bewithin normal limits.

14. Negative serum pregnancy test at the time of first dose for women of childbearing potential (WOCBP). For WOCBP, adequate contraception must be used throughout the study. For this study, acceptable methods of contraception include a reliable intrauterine device or a spermicide in combination with a barrier method. Women who are already on hormonal forms of birth control may continue that treatment but must also use a barrier method.
15. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments.
16. Patient must be willing to undergo breast biopsies as required by the study protocol.

8.2 Exclusion Criteria:

1. Radiation therapy within 2 weeks; or chemotherapy or non-cytotoxic investigational agents within 2 weeks of initiating study treatment.
2. Evidence of New York Heart Association class III or greater cardiac disease.
3. History of myocardial infarction, stroke, ventricular arrhythmia, or symptomatic conduction abnormality within 12 months.
4. History of congenital QT prolongation.
5. QT >500.
6. Concurrent severe or uncontrolled medical disease (i.e., active systemic infection, diabetes, hypertension, coronary artery disease, congestive heart Failure or major surgery) that, in the opinion of the Investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study.
7. Symptomatic central nervous system metastases.
8. The patient must be stable after radiotherapy for ≥2 weeks and off corticosteroids for ≥1 week.
9. Pregnant or nursing women.
10. Hypersensitivity or intolerance to Quinolones, Chloroquine, Paclitaxel, Docetaxel, Abraxane, Ixabepilone or other Taxane like drugs.
11. Active diagnosis of psoriasis or currently receiving treatment for psoriasis.
12. Alcoholism or hepatic disease.
13. History of epilepsy or seizures in the past 20 years.
14. Receiving concurrent treatment with prohibited medications (See appendix E) Examples include: ampicillin, antacids, cimetidine, cyclosporine, kaolin, magnesium trisilicate, coumarin-type anticoagulants, macrolide antibiotics (e.g., clarithromycin, isoniazid, and erythromycin), anti-HIV agents (e.g., ritonavir and delavirdine), antidepressants (e.g. fluoxetine and fluvoxamine), calcium channel blockers (e.g. verapamil and diltiazem), steroids and their modulators (e.g., gestodene, raloxifene, and mifepristone), and several herbal and dietary components (e.g. bergamottin and glabridin).
15. Severe renal insufficiency (CrCl <30mL/min [Cockcroft and Gault]).
16. History of gastrointestinal bleeding, ulceration, or perforation.

17. Concurrent use of potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, clarithromycin, atanazir, indinavir, nefazodone, neflinavir, ritonavir, saquinavir, telithromycin, and voriconazole.
18. Concurrent use of potent CYP3A4 inducers, such as dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbitol, and St. John's wort.
19. Used an investigational drug within 14 days preceding the first dose of study medication.

9.0 Treatment Plan/Methods

This is a phase II trial; 47 patients with diagnosis of with metastatic breast cancer, who have failed anthracycline chemo base therapy, will be enrolled in the study. Patients will receive Chloroquine (C) together with Taxane or Taxane-like (Paclitaxel, Docetaxel, Abraxane, Ixabepilone) (T) Chemo Agents.

The study population will include subjects ≥ 18 years of age with histologically confirmed metastatic breast carcinoma. Subjects will have a medical history and physical assessment to include concomitant medication, standard of care breast cancer staging including mammogram, ultrasound, bone scan, chest x-ray or chest CT as well as blood tests for Complete Blood Count (CBC) with differentials, Complete Metabolic Panel (CMP). Prior to starting treatment, subjects will have a research biopsy of accessible sites. The study doctor will determine if the subject qualified to be enrolled in this study. Study treatment may continue as determined by the investigator until disease progression, intolerable AEs, death, voluntary withdrawal from the study by the patient, or discontinuation of the study by the sponsor.

9.0.1 Treatment (Physician Choice)

Subjects eligible for treatment will receive treatments per NCCN guidelines:
A: Chloroquine 250mg po daily together with Paclitaxel 175 mg/m^2 three hours infusion every two or three weeks or Paclitaxel 80 mg/m^2 weekly. Or
B: Chloroquine 250mg po daily together with Taxotere 75 mg/m^2 (or 100mg/m^2 in advanced breast cancer patients) administered intravenously over one hour every three weeks. Or
C: Chloroquine 250mg po daily together with Abraxane 260 mg/m2 administered intravenously over 30 minutes every three weeks or 100mg/m^2 administered weekly. Or
D: Chloroquine 250mg po daily together with Ixabepilone is 40 mg/m^2 administered intravenously over three hours every three weeks. Doses for patients with body surface area (BSA) greater than 2.2 m^2 should be calculated based on 2.2 m^2.

Infusion times for chemotherapy are approximate and can vary slightly. Infusion time can be slowed for the safety of the patient. Dose reductions are allowed at the discretion of the investigator for patient safety.

Subjects will be premedicated approximately 1 hour before the infusion. Standard anti-emetics for moderately emetogenic regimen, together with standard premedication will be prescribed with chemotherapy. Recommended prophylaxis for the taxane and taxane-like chemo agent includes:

- Paclitaxel premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before Paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to Paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before Paclitaxel or use premedication per institutional standards.
- Taxotere premedicated may consist of oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to Taxotere administration or use premedication per institutional standards.

- Abraxane, no premedication is needed.
- Ixabepilone premedication may consist of H1 antagonist (e.g., diphenhydramine 50 mg orally or equivalent) and a H2 antagonist (e.g., ranitidine 150 - 300 mg orally or equivalent). Or use premedication per institutional standards.

9.1 DRUG INFORMATION AND MODIFICATIONS:

9.1.1 CHLOROQUINE

ARALEN, chloroquine phosphate, USP, is a 4-aminoquinoline compound for oral administration. It is a white, odorless, bitter tasting, crystalline substance, freely soluble in water. ARALEN is an antimalarial and amebicidal drug.

Chemically, it is 7-chloro-4-[[4-(diethylamino)-1-methylbutyl]amino]quinoline phosphate (1:2) and has the following structural formula:

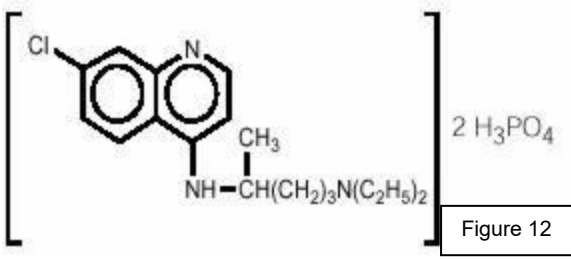


Figure 12

Each tablet contains 250 mg of chloroquine phosphate USP, equivalent to 150 mg chloroquine base.

Inactive Ingredients: Carnauba Wax, Colloidal Silicon Dioxide, Dibasic Calcium Phosphate, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Pregelatinized Starch, Sodium Starch Glycolate, Stearic Acid, Titanium Dioxide.

CLINICAL PHARMACOLOGY

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract, and only a small proportion of the administered dose is found in the stools. Approximately 55% of the drug in the plasma is bound to nondiffusible plasma constituents. Excretion of chloroquine is quite slow, but is increased by acidification of the urine. Chloroquine is deposited in the tissues in considerable amounts. In animals, from 200 to 700 times the plasma concentration may be found in the liver, spleen, kidney, and lung; leukocytes also concentrate the drug. The brain and spinal cord, in contrast, contain only 10 to 30 times the amount present in plasma. Chloroquine undergoes appreciable degradation in the body. The main metabolite is desethylchloroquine, which accounts for one fourth of the total material appearing in the urine; bisdesethylchloroquine, a carboxylic acid derivative, and other metabolic products as yet uncharacterized are found in small amounts. Slightly more than half of the urinary drug products can be accounted for as unchanged chloroquine.[47]

Microbiology

Mechanism of Action

Chloroquine is an antimalarial agent. While the drug can inhibit certain enzymes, its effect is believed to result, at least in part, from its interaction with DNA. However, the mechanism of plasmodicidal action of chloroquine is not completely certain.

Activity *in vitro* and *in vivo*

Chloroquine is active against the erythrocytic forms of *Plasmodium vivax. Plasmodium malariae*, and susceptible strains of *Plasmodium falciparum* (but not the gametocytes of *P. falciparum*). It is not effective against exoerythrocytic forms of the parasite. *In vitro* studies with trophozoites of *Entamoeba histolytica* have demonstrated that chloroquine also possesses amebicidal activity comparable to that of emetine.

Drug Resistance
Resistance of *Plasmodium falciparum* to chloroquine is widespread and cases of *Plasmodium vivax* resistance have been reported.

INDICATIONS AND USAGE
ARALEN is indicated for the suppressive treatment and for acute attacks of malaria due to *P. vivax, P.malariae, P. ovale*, and susceptible strains of *P. falciparum.* The drug is also indicated for the treatment of extraintestinal amebiasis.
ARALEN does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exoerythrocytic forms of the parasite, nor will it prevent vivax or malariae infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum*.[47]

CONTRAINDICATIONS
Use of this drug is contraindicated in the presence of retinal or visual field changes either attributable to 4-aminoquinoline compounds or to any other etiology, and in patients with known hypersensitivity to 4-aminoquinoline compounds. However, in the treatment of acute attacks of malaria caused by susceptible strains of plasmodia, the physician may elect to use this drug after carefully weighing the possible benefits and risks to the patient.

WARNINGS
It has been found that certain strains of *P. falciparum* have become resistant to 4-aminoquinoline compounds (including chloroquine and hydroxychloroquine). Chloroquine resistance is widespread and, at present, is particularly prominent in various parts of the world including sub-Saharan Africa, Southeast Asia, the Indian subcontinent, and over large portions of South America, including the Amazon basin. Before using chloroquine for prophylaxis, it should be ascertained whether chloroquine is appropriate for use in the region to be visited by the traveler. Chloroquine should not be used for treatment of *P. falciparum* infections acquired in areas of chloroquine resistance or malaria occurring in patients where chloroquine prophylaxis has failed. Patients infected with a resistant strain of plasmodia as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia should be treated with another form of antimalarial therapy. Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinoline therapy. Retinopathy has been reported to be dose related. When prolonged therapy with any antimalarial compound is contemplated, initial (base line) and periodic ophthalmologic examinations (including visual acuity, expert slit-lamp, funduscopic, and visual field tests) should be performed. If there is any indication (past or present) of abnormality in the visual acuity, visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) which are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress even after cessation of therapy. All patients on long-term therapy with this preparation should be questioned and examined periodically, including testing knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug. A number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 g or 1 g chloroquine phosphate in one 3-year-old child). Patients should be strongly warned to keep this drug out of the reach of children because they are especially sensitive to the 4-aminoquinoline compounds.
Use of ARALEN in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria the condition may be exacerbated. The drug should not be used

in these conditions unless in the judgment of the physician the benefit to the patient outweighs the potential risks. [47]

Usage in Pregnancy

Radioactively tagged chloroquine administered intravenously to pregnant pigmented CBA mice passed rapidly across the placenta and accumulated selectively in the melanin structures of the fetal eyes. It was retained in the ocular tissues for five months after the drug had been eliminated from the rest of the body. There are no adequate and well-controlled studies evaluating the safety and efficacy of chloroquine in pregnant women. Usage of chloroquine during pregnancy should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the potential risk to the fetus.

Hematological Effects/Laboratory Tests

Complete blood cell counts should be made periodically if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuance of the drug should be considered.

The drug should be administered with caution to patients having G-6-PD (glucose-6 phosphate dehydrogenase) deficiency.

Auditory Effects

In patients with preexisting auditory damage, chloroquine should be administered with caution. In case of any defects in hearing, chloroquine should be immediately discontinued, and the patient closely observed.

Hepatic Effects

Since this drug is known to concentrate in the liver, it should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs.

Central Nervous System Effects

Patients with history of epilepsy should be advised about the risk of chloroquine provoking seizures.

Drug Interactions

Antacids and kaolin: Antacids and kaolin can reduce absorption of chloroquine; an interval of at least 4 hours between intake of these agents and chloroquine should be observed.

Cimetidine: Cimetidine can inhibit the metabolism of chloroquine, increasing its plasma level. Concomitant use of cimetidine should be avoided.

Ampicillin: In a study of healthy volunteers, chloroquine significantly reduced the bioavailability of ampicillin. An interval of at least two hours between intake of this agent and chloroquine should be observed.

Cyclosporine: After introduction of chloroquine (oral form), a sudden increase in serum cyclosporine level has been reported. Therefore, close monitoring of serum cyclosporine level is recommended and, if necessary, chloroquine should be discontinued.

Mefloquine: Co-administration of chloroquine and mefloquine may increase the risk of convulsions.

The blood concentrations of chloroquine and desethylchloroquine (the major metabolite of chloroquine, which also has antimalarial properties) were negatively associated with log antibody titers. Chloroquine taken in the dose recommended for malaria prophylaxis can reduce the antibody response to primary immunization with intradermal human diploid-cell rabies vaccine. [47]

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants from chloroquine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the potential clinical benefit of the drug to the mother. The excretion of chloroquine and

the major metabolite, desethylchloroquine, in breast milk was investigated in eleven lactating mothers following a single oral dose of chloroquine (600 mg base). The maximum daily dose of the drug that the infant can receive from breastfeeding was about 0.7% of the maternal start dose of the drug in malaria chemotherapy. Separate chemoprophylaxis for the infant is required.

Geriatric Use

Clinical studies of chloroquine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

ADVERSE REACTIONS

Special Senses: Ocular: Irreversible retinal damage in patients receiving long-term or high-dosage 4-aminoquinoline therapy; visual disturbances (blurring of vision and difficulty of focusing or accommodation); nyctalopia; scotomatous vision with field defects of paracentral, pericentral ring types, and typically temporal scotomas, e.g., difficulty in reading with words tending to disappear, seeing half an object, misty vision, and fog before the eyes. Reversible corneal opacities have also been reported.

Auditory: Nerve type deafness; tinnitus, reduced hearing in patients with preexisting auditory damage. [47]

Musculoskeletal system: Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups, which may be associated with mild sensory changes, depression of tendon reflexes and abnormal nerve conduction, have been noted.

Gastrointestinal system: Hepatitis, increased liver enzymes, anorexia, nausea, vomiting, diarrhea, abdominal cramps.

Skin and appendages: Rare reports of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and similar desquamation-type events. Pleomorphic skin eruptions, skin and mucosal pigmentary changes; lichen planus-like eruptions, pruritus, urticaria, anaphylactic/anaphylactoid reaction including angioedema, photosensitivity and hair loss and bleaching of hair pigment.

Hematologic system: Rarely, pancytopenia, aplastic anemia, reversible agranulocytosis, thrombocytopenia and neutropenia.

Nervous system: Convulsive seizures, mild and transient headache, polyneuritis. Neuropsychiatric changes including psychosis, delirium, anxiety, agitation, insomnia, confusion, hallucinations, personality changes, and depression.

Cardiovascular system: Rarely, hypotension, electrocardiographic change (particularly, inversion or depression of the T-wave with widening of the QRS complex), and cardiomyopathy.

OVERDOSAGE

Symptoms

Chloroquine is very rapidly and completely absorbed after ingestion. Toxic doses of chloroquine can be fatal. Toxic symptoms can occur within minutes. These consist of headache, drowsiness, visual disturbances, nausea and vomiting, cardiovascular collapse, shock and convulsions followed by sudden and early respiratory and cardiac arrest. Hypokalemia has been observed with arrhythmias in cases of intoxication. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

Treatment

Treatment is symptomatic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital) or gastric lavage until the stomach is completely emptied. If finely powdered, activated charcoal is introduced by stomach tube, after lavage, and within 30 minutes after ingestion of the antimalarial, it may inhibit further intestinal

absorption of the drug. To be effective, the dose of activated charcoal should be at least five times the estimated dose of chloroquine ingested. Convulsions, if present, should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultra short-acting barbiturate may be tried but, if due to anoxia, it should be corrected by oxygen administration and artificial respiration. Monitor ECG. In shock with hypotension, a potent vasopressor should be administered. Replace fluids and electrolytes as needed. Cardiac compressing or pacing may be indicated to sustain the circulation. Because of the importance of supporting respiration, tracheal intubation or tracheostomy, followed by gastric lavage, may also be necessary. Peritoneal dialysis and exchange transfusions have also been suggested to reduce the level of the drug in the blood. Intervention options can involve: diazepam for life-threatening symptoms, seizures and sedation, epinephrine for treatment of vasodilation and myocardial depression, potassium replacement with close monitoring of serum potassium levels. A patient who survives the acute phase and is asymptomatic should be closely observed for at least six hours. Fluids may be forced, and sufficient ammonium chloride (8 g daily in divided doses for adults) may be administered for a few days to acidify the urine to help promote urinary excretion in cases of both overdosage or sensitivity. [22]

Dosage in Renal Failure

In patients with severe renal failure (GFR less than 10 milliliters/minute) 50% of the normal dose should be administered. If prolonged treatment is necessary, the dosage should be further reduced to 50 to 100 milligrams/day.

Dosage in Hepatic Insufficiency

Thirty percent to 50% of the administered dose is modified by the liver, and appropriate dosage adjustment is necessary. Serum drug monitoring may be useful. [22]

9.1.2 Paclitaxel

SYNONYM(S): NSC-125973

COMMON TRADE NAMES: generic available, ONXOL® (USA), TAXOL®

CLASSIFICATION: antimicrotubule agent, cytotoxic

MECHANISM OF ACTION: Paclitaxel is an antimicrotubule agent that promotes the assembly and stabilization of microtubules from tubulin dimers. Late G2 mitotic phase is inhibited and thus cell replication is inhibited. Paclitaxel also can distort mitotic spindles resulting in chromosomal damage. [48]

PHARMACOKINETICS:

Distribution	biphasic; initial rapid distribution to the peripheral compartment, then a slow efflux of paclitaxel from the peripheral compartment; widely distributed into body fluids and tissues; affected by dose and duration of infusion	
Metabolism		
	volume of distribution	no
	plasma protein binding	198-688 L/m^2; varies with dose and infusion time
	hepatic via the cytochrome P450 isozymes CYP2C8/9 and CYP3A4	89-98%
Excretion	active metabolite(s)	
	inactive metabolite(s)	primarily 6α-hydroxypaclitaxel
	elimination follows non-linear (saturable) pharmacokinetics; high concentrations found in bile	yes
Gender	urine	
	feces	14% (1.3-12.6% as unchanged drug)

	terminal half life	71% (5% as unchanged drug)	
	clearance	3.0-52.7 h; varies with dose and infusion time (e.g., 3 h infusion of 175 mg/m^2: 9.9 h)	
	no information found	11.6-24.0 L/h/m^2; varies with dose and infusion time (e.g., 3 h infusion of 175 mg/m^2: 12.4 L/h/m^2)	
Elderly	clearance		
Children	terminal half life	11.4-16.2 L/h/m^2	Table 3

SPECIAL PRECAUTIONS:

Hypersensitivity reactions (HSR): Paclitaxel infusions may be associated with acute hypersensitivity reactions; incidence is significantly reduced by premedication and increased infusion times

Carcinogenicity: Not yet studied.

Elderly patients are at an increased risk for developing toxicities (e.g., arthralgia, myalgia, neutropenia, neuropathy).

Mutagenicity: Paclitaxel was not mutagenic in the Ames test. Paclitaxel was clastogenic in the mammalian in vitro and in vivo chromosome tests.

Fertility: The effects of paclitaxel on fertility have not been established. Women of childbearing potential should be counseled to avoid pregnancy.

Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk. [48]

SIDE EFFECTS:

ORGAN SITE	SIDE EFFECT	ONSET			
I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
allergy/immunology	**hypersensitivity reactions (severe 1%)**	I			
blood/bone marrow/ febrile neutropenia	anemia (62%, severe 6%)		E		
	neutropenia (severe 6-21%); nadir 8-11 days, recovery 15-21 days	I			
	thrombocytopenia (6%)	I			
cardiovascular (arrhythmia)	arrhythmias (1%) (e.g., asymptomatic ventricular tachycardia, atrial fibrillation, supraventricular tachycardia, junctional tachycardia)	I			
	bradycardia (25%); during infusion, transient	I			
cardiovascular (general)	electrocardiogram abnormalities (23%)	I			
	edema (21%)		E		
	hypertension (1%)	I			
	hypotension (24%); during infusion, transient	I			
	myocardial infarction (rare)			D	
constitutional symptoms					
dermatology/skin	extravasation hazard: irritant				

ORGAN SITE	SIDE EFFECT	ONSET			
I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
	alopecia (87%); usually complete, generally occurs 14-21 days after administration of paclitaxel with a sudden onset, often occurring in a single day[9]		E		
	flushing (28%)	I			
	nail and skin changes (2%); mild, transient		E		
	radiation recall reaction (rare)		E		
	rash (12%)	I			
gastrointestinal	emetogenic potential: low				
	anorexia (25%)		E		
	constipation (18%)		E		
	diarrhea (38%)	I			
	intestinal obstruction (4%)		E		
	mucositis (31%); more common with 24 h infusion		E		
	nausea (52%); mild to moderate	I			
	stomatitis (15%); most common at doses >390 mg/m^2		E		
	taste perversion		E		
	vomiting (5-6%); mild to moderate	I			
hepatic	hepatic necrosis and hepatic encephalopathy (rare)			D	
infection	febrile neutropenia (12%)	I			
neurology	ataxia (<1%)		E		
	encephalopathy (rare)		E		
	ethanol intoxication	I			
	seizures (rare)		E		
	myopathy (25-50%)		E		
	peripheral neuropathy (64%, severe 4%)		E		
metabolic/laboratory	mild increase in liver enzymes (18%)	I			
ocular/visual	optic nerve and/or visual disturbances (rare)		E		
pain	**arthralgia/myalgia (54%, severe 12%)**	I	E		
pulmonary	interstitial pneumonia, lung fibrosis (rare)			D	
vascular	pulmonary embolism (rare)	I			
	phlebitis (2%)	I			

Table 4

Hypersensitivity reactions (HSR) are common with paclitaxel and appear to be due to a nonimmunologically-mediated release of histamine and other vasoactive substances. The exact cause is not known but may result from either the Cremophor EL in the paclitaxel injection or from the paclitaxel itself. HSR most often occur in the first hour of an infusion (75% occur within the first 10 minutes). The frequency and severity of these reactions are not affected by the dose or schedule of paclitaxel administration. Delayed onset of urticarial rash, 7-10 days following completion of a course of treatment, has been seen in some Kaposi's sarcoma patients.

Incidence of HSR are significantly reduced by premedication. Corticosteroids (e.g., dexamethasone), histamine H_1-antagonists (e.g., diphenhydramine) and H_2-antagonists (e.g., ranitidine) should be administered prior to paclitaxel administration to minimize the potential for anaphylaxis. The following is one suggested regimen for adults:

- 45 minutes before paclitaxel, dexamethasone 20 mg IV
- 30 minutes before paclitaxel, diphenhydramine 50 mg IV and ranitidine 50 mg IV.

A more protracted premedication scheme, which may be more effective, particularly where a patient has exhibited HSR would be: 12 hours and 6 hours before paclitaxel, dexamethasone 20 mg po and then following the above premedication regime. In the event of a treatment delay (e.g., admixture is unavailable), additional doses are required. In premedicated patients, symptoms of HSR are reported in as many as 41%, although severe HSR occur in less than 2% of patients.

The occurrence of HSR does not preclude rechallenge with paclitaxel. If there is a hypersensitivity reaction, the patient may be rechallenged after further premedication and with close monitoring. Prolonging the infusion to $\geq$ 6 hours may decrease the incidence of hypersensitivity reactions; 24, 96 and 120 hour infusions have been studied and show decreased HSR with increased infusion times.

Treatment for hypersensitivity reactions, including general management, and management of hypotension, dyspnea and bronchospasm can be found in the BC Cancer Agency Protocol Summary of Hypersensitivity Reactions to Chemotherapeutic Agents (SCDRUGRX). See below for general management.

General Management: It is recommended that patients are assessed by a physician if having a reaction requiring the administration of medications or as patient condition warrants. [48]

Moderate e.g., moderate rash, flushing, pruritus, mild dyspnea, chest discomfort, abdominal discomfort, lower back pain, mild hypotension	Stop infusion. Give diphenhydramine 25-50 mg IV and/or hydrocortisone sodium succinate 100 mg per physician orders. After recovery of symptoms, resume infusion at a rate per protocol. If no direction in protocol consider resuming at 25% of previous rate for at least 5 minutes, 50% for at least 5 minutes, 75% for at least 5 minutes and then full rate if no reaction. Depending on severity of reaction, may increase to full rate at physician's discretion. Premedication for all future cycles (see Prophylaxis section in SCDRUGRX). Initiate infusion at slower rate (consider 50% of full rate) per physician orders.
Severe (potentially life threatening) i.e., to be used if reaction escalates (e.g., one or more of respiratory distress requiring treatment, angioedema, hypotension requiring therapy)	Stop infusion and do not restart. Give diphenhydramine 50 mg IV push and/or hydrocortisone sodium succinate 100 mg IV push per physician orders. Oxygen if needed for dyspnea (see SCDRUGRX). Normal saline if needed for hypotension (see SCDRUGRX). Epinephrine or bronchodilators if indicated (see SCDRUGRX). Either permanently discontinue the drug or attempt to retreat on another occasion after premedication (see SCDRUGRX) and using slower infusion rate. Initiate Emergency Response System appropriate for facility if patient condition warrant.

Table 5

IF there is a true anaphylactic reaction with paclitaxel despite premedication and a slow initial infusion rate the patient should not have a further rechallenge.

Very rarely, fatal reactions have occurred in patients despite pre-treatment. Docetaxel has been successfully substituted in some patients who experienced severe HSR with paclitaxel; however, cross-sensitivity has also been reported.

Arthralgia/myalgia is dose and schedule dependent; worse with higher doses and shorter infusions. The symptoms are usually transient, occur within two or three days after paclitaxel

administration, and resolve after a few days. If arthralgia/myalgia from paclitaxel is grade 2 (moderate) or higher and is not relieved by adequate doses of NSAIDS or acetaminophen with codeine a suggested symptomatic treatment includes:

- gabapentin 300 mg po on day prior to paclitaxel, 300 mg po bid on treatment day and then 300 mg po tid x 7-10 days
- prednisone 10 mg po bid x 5 days starting 24 hours post-paclitaxel

Peripheral neuropathy is usually sensory in nature. Paclitaxel-induced neurotoxicity often appears as mild paresthesia characterized by numbness and tingling in a stocking-and-glove distribution. Perioral numbness may also occur, and many patients experience burning pain particularly in the feet. Onset may be rapid, occurring within a few days of an infusion. Frequency and severity are related to cumulative doses; toxicity may be dose-limiting. Sensory manifestations usually improve or resolve several months after discontinuing paclitaxel. Pre-existing neuropathies resulting from prior therapies are not a contraindication for treatment with paclitaxel; however, the incidence of paclitaxel-related neuropathy appears to be increased in this population of patients.

Bradycardia and hypotension during paclitaxel administration is usually asymptomatic and generally does not require treatment. In some cases, paclitaxel administration may have to be interrupted or discontinued. Based on nursing experience with paclitaxel administration, and consultation with medical oncology and pharmacy, the BC Cancer Agency has found that clinical observation of patients by nurses for early signs of a reaction is more valuable than taking vital signs every15 minutes. Severe cardiac conduction abnormalities have rarely occurred during paclitaxel therapy. If patients develop significant conduction abnormalities during administration, appropriate treatment should be administered and continuous electrocardiographic monitoring should be performed during subsequent infusions.

Ethanol is contained in the paclitaxel formulation at a concentration of 396 mg/mL. Consideration should be given to possible CNS effects including impaired ability to drive and operate machinery.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
doxorubicin	increased doxorubicin efficacy and toxicity	decreased clearance of doxorubicin	monitor for increased cardiotoxicity (e.g., congestive heart failure) or consider using docetaxel instead of paclitaxel (docetaxel does not appear to share this same interaction potential)
epirubicin	toxicity of both agents may be increased when given concurrently, regardless of which drug is given first; lower neutrophil and platelet nadirs, and slower neutrophil recovery, have been observed	increased levels of epirubicin metabolites, decreased paclitaxel clearance	separate administration by 24 hours if possible
gemcitabine	delayed, moderate, possible; increased gemcitabine efficacy and toxicity	unknown	monitor for gemcitabine toxicity during coadministration
platinum derivatives (e.g., carboplatin, cisplatin)	increased paclitaxel toxicity; paradoxical decreased platelet toxicity from carboplatin	decreased clearance of paclitaxel	paclitaxel should be given first when administering as sequential infusions with either of these drugs

AGENT	EFFECT	MECHANISM	MANAGEMENT
trastuzumab[53]	may increase efficacy of paclitaxel	unknown	preferred method is to give trastuzumab first when administering as sequential infusions
warfarin[52]	delayed, moderate suspected; the anticoagulant effect of warfarin may be increased	decreased warfarin metabolism	monitor coagulation parameters during coadministration or consider use of LMWH during course of chemotherapy

Table 6

Paclitaxel is a major CYP2C8/9 substrate; therefore drugs that are CYP2C8/9 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin and secobarbital) may decrease the levels/effects of paclitaxel. Likewise, drugs that are CYP2C8/9 inhibitors (e.g., fluconazole, gemfibrozil, ketoconazole, NSAIDS and sulfonamides) may increase the levels/effects of paclitaxel.
Paclitaxel is a major CYP3A4 substrate, therefore drugs that are CYP3A4 inducers (e.g., aminoglutethimide, carbamazepine, nafcillin, phenobarbital and phenytoin) may decrease the levels/effects of paclitaxel. Herbs that are CYP3A4 inducers (e.g., St John's Wort) may also decrease the levels/effects of paclitaxel. Likewise, drugs that are CYP3A4 inhibitors (e.g., azole antifungals, ciprofloxacin, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, propofol, protease inhibitors, quinidine and verapamil) may increase the levels/effects of paclitaxel. Paclitaxel is also a weak CYP3A4 inducer.

DOSAGE GUIDELINES:

If myelosuppression modify dosage as follows:

PLATELET COUNT ($\times 10^9$/L)	ABSOLUTE NEUTROPHIL (ANC)* ($\times 10^9$/L)			
	$\geq$ 1.8	1.5-1.8	1.0-1.5	<1.0
$\geq$ 100	100%	75%	50%	0%
70-100	75%	75%	50%	0%
50-70	50%	50%	50%	0%
<50	0%	0%	0%	0%

Table 7

* ANC = WBC x (% polys + % stabs)
** 0% Indicates treatment should be postponed a week until the counts return to a level at which drugs may be given.

Concurrent radiation: Generally not administered concurrently due to additive toxicity.

Dosage in hepatic failure:

Suggested guidelines for first course; subsequent courses should be based on individual tolerance			
paclitaxel 24 h infusion:			
ALT	**bilirubin**		**dose**
<2 X ULN	and	<26 µmol/L	135 mg/m^2
2 to <10 X ULN	and	<26 µmol/L	100 mg/m^2
<10 x ULN	and	27-128 µmol/L	50 mg/m^2
>10 x ULN	or	>128 µmol/L	not recommended
paclitaxel 3 h infusion:			
ALT	**bilirubin**		**dose**
<10 X ULN	and	<1.25 x ULN	175 mg/m^2
<10 X ULN	and	1.26-2.0 x ULN	135 mg/m^2
<10 X ULN	and	2.01-5.0 x ULN	90 mg/m^2
>10 x ULN	or	>5.0 x ULN	not recommended

Table 8

Dosage in dialysis: No significant removal by hemodialysis. [48]

9.1.3 Docetaxel

DRUG NAME: Docetaxel

SYNONYM(S): **RP56976**

COMMON TRADE NAME(S): TAXOTERE®

CLASSIFICATION: Mitotic inhibitor, cytotoxic

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Docetaxel is a semi-synthetic drug derived from precursor extracted from the needles of the European yew tree, Taxus baccata. It acts by disrupting the microtubular network that is essential for mitotic and interphase cellular functions. It promotes the assembly of tubulin into stable microtubules and inhibits their disassembly, causing inhibition of cell division and eventual cell death. Both docetaxel and paclitaxel bind to the same microtubule site, although the affinity of docetaxel is 1.9-fold higher. Cross-resistance between docetaxel and paclitaxel does not occur consistently. Docetaxel is a radiation-sensitizing agent. It is cell cycle phase-specific (G2/M phase). [49]

PHARMACOKINETICS: Interpatient variability	wide interpatient variability, probably due to interpatient differences in cytochrome P450 3A4 (CYP3A4) activity.	
Distribution	distributed to all tissues and organs except the brain in animal studies	
	Cross blood brain barrier?	Very low levels were found in the brain in animal studies. In a single patient with leptomeningeal carcinomatosis, docetaxel was detected in CSF 2 hours after cessation of docetaxel infusion.
	volume of distribution	113 L
	plasma protein binding	> 95%
Metabolism	CYP3A involved in docetaxel metabolism in vitro	
	active metabolite(s)	none
	inactive metabolite(s)	one major and 3 minor
Excretion	primarily biliary/fecal elimination	
	urine	6% recovered in urine over 7 days
	feces	75% recovered in feces over 7 days, 80% of which was excreted during the first 2 days; < 8% was unchanged docetaxel.
	terminal half life	11.1 h
	clearance	21 L/h/m^2
Gender	no clinically significant difference	
Elderly	no clinically significant difference	

Table 9

SPECIAL PRECAUTIONS:

Contraindicated in patients with a history of hypersensitivity reaction to docetaxel or to drugs formulated with polysorbate 80. Patients with prior severe hypersensitivity reactions should generally not be rechallenged with docetaxel. However, in patients with objective tumor responses and without other options to docetaxel therapy, re-treatment may be attempted with extreme caution and aggressive premedication by experienced practitioners. Contraindicated in patients with severe liver impairment. Patients hypersensitive to paclitaxel may also react to docetaxel.

Preexisting effusions: Patients with preexisting effusion should be closely monitored from the first dose for the possible exacerbation of the effusions.

Liver impairment: Patients treated with docetaxel 100 mg/m^2 are at a higher risk of developing severe adverse reactions if they have elevated transaminase (ALT and/or AST greater than 1.5 times the upper limit of normal [ULN]) and alkaline phosphatase (greater than 2.5 times ULN). Liver impairment reduces clearance and increases systemic exposure to docetaxel. Adverse reactions include life-threatening sepsis and gastrointestinal hemorrhage, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia.
Alcohol abuse: When docetaxel is used in patients who abuse alcohol, or have abused alcohol, the risk of severe neurotoxic reactions may be increased.
Carcinogenicity: No information found.
Mutagenicity: Not mutagenic in Ames test or mammalian in vitro mutation test. Clastogenic in mammalian in vitro and in vivo chromosome tests.
Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Breastfeeding is not recommended due to the potential secretion into breast milk. [49]

SIDE EFFECTS: ORGAN SITE	SIDE EFFECT
allergy/immunology	hypersensitivity reaction (21%, severe 4%); see paragraph following **Side Effects** table
	moderate immunosuppression
blood/bone marrow febrile neutropenia	anemia (90%, severe 9%)
	death, septic (1.7%)
	death, nonseptic (0.3%)
	febrile neutropenia (11%)
	infection with neutropenia (severe 6%)
	leukocytopenia (96%, severe 75%)
	neutropenia (96%, severe 32%) nadir 8 days, duration of severe neutropenia 7 days
	thrombocytopenia (8%)
cardiovascular (arrhythmia)	dysrhythmia (2%, severe 0.4%)
	tachycardia (1%)
cardiovascular (general)	fluid retention, with premedication (52%, severe 6%); see paragraph following **Side Effects** table
	fluid retention, without premedication (82%, severe 22%); see paragraph following **Side Effects** table
	heart failure (0.3%)
	hypertension (2%)
	hypotension (3%, severe 0.5%)
constitutional symptoms	fatigue, 3-weekly schedule (62%, severe 13%) ***fatigue, weekly schedule*** (72%, severe 14%)26
	fever (32%, severe 2%)
dermatology/skin	*extravasation hazard:* irritant27
	alopecia (56-85%, severe 0.5%)28,29; see paragraph following **Side Effects** table
	injection site reactions (6%); see paragraph following **Side Effects** table
	nail changes (19-51%, severe 2-22%)2,30-32; see paragraph following **Side Effects** table
	hand-foot skin reaction (rare)1; see paragraph following **Side Effects**

	table
	radiation recall reaction33,34
	rash/pruritus (48%, severe 5%); see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low moderate9
	diarrhea (39%, severe <5%)
	nausea (39%, severe <5%)
	perforation (rare)
	stomatitis (42%, severe 6%)
	vomiting (22%, severe <5%)
hemorrhage	bleeding episode (1%)
	bleeding episode with thrombocytopenia (0.1%)
infection	infection, including sepsis and pneumonia (22%)
metabolic/laboratory	elevated AST, ALT, bilirubin, and alkaline phosphatase (<2%)
neurology	neuropathy, motor (14%%, severe 4%); see paragraph following **Side Effects** table
	neuropathy, sensory (49%, severe 4%); see paragraph following **Side Effects** table
ocular/visual	tearing/watery eyes, weekly schedule (52%)13; see paragraph following **Side Effects** table
pain	arthralgia (9%, severe 0.6%)
	myalgia (19%, severe 2%)

Table 10

Pretreatment administration of dexamethasone is recommended to decrease the frequency and severity, and to delay the onset of docetaxel-induced fluid retention. Dexamethasone also reduces the severity of docetaxel-induced hypersensitivity reactions and cutaneous toxicity.
3-weekly regimen: A commonly used regimen consists of dexamethasone 8 mg PO twice a day for 3 consecutive days starting one day prior to each docetaxel infusion. This regimen has also been shown to decrease the occurrence of severe stomatitis and infection.2 Patients must receive a minimum of 3 doses of dexamethasone prior to docetaxel treatment. If dexamethasone has not been taken prior to treatment, it should be started and the docetaxel infusion delayed until the following day. If treatment delay is not possible, diphenhydramine 50 mg IV and dexamethasone 10 mg IV may be given 30 minutes before starting docetaxel.35 Note that this premedication regimen has not been shown to reduce the incidence and severity of fluid retention, but is only an attempt to ameliorate hypersensitivity reactions. The patient should then be instructed to take dexamethasone 8 mg PO twice a day for two days.
Weekly regimen: An abbreviated course of dexamethasone may be used for the “weekly” schedule (i.e., 8-week cycle). This regimen consists of dexamethasone 8 mg PO for 3 doses starting the night before, morning of and evening after treatment (total dose, 24 mg/week). Alternatively, a single 8 mg dexamethasone dose 1 hour prior to docetaxel administration may be used.
Dexamethasone dose for children: Dexamethasone in a dose of 3 mg/m² PO or IV for two doses 12 hours and 6 hours prior to the dose of docetaxel may be used for children.
Hypersensitivity reactions are most likely to occur during the first two cycles of docetaxel treatment, generally within the first few minutes after the infusion is started. Signs and symptoms usually abate within 15 minutes after the infusion is stopped.3 The most frequent minor manifestations were flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever or chills. If minor reactions occur, therapy with docetaxel does not have to be discontinued. For severe reactions such as hypotension requiring treatment, bronchospasm, and generalized rash/erythema; stop the docetaxel, and have a physician assess the patient and order appropriate treatment. [49]

Rechallenge after severe hypersensitivity reaction: Patients who have developed severe hypersensitivity reactions should generally not be rechallenged with docetaxel. However, in patients with objective tumor responses and without other options to docetaxel therapy, re-treatment may be attempted with extreme caution and aggressive premedication by experienced practitioners. It is recommended that a slower rate of infusion be used. One patient experienced major hypersensitivity symptoms during the first two cycles of docetaxel therapy despite prophylaxis with a corticosteroid and a histamine H1 blocking antagonist. Treatment was continued without further difficulty after sodium cromoglycate (400 mg PO four times a day, starting immediately after the second cycle) was added to the prophylactic regimen.

Fluid retention includes edema, and less frequently, pleural effusion, ascites, pericardial effusion and weight gain. Fluid retention occurs in 52% of patients receiving dexamethasone premedication, and in 82% of patients without premedication. It usually begins at the lower extremities and may become generalized with a weight gain of 3 kg or more. Fluid retention is not accompanied by acute episodes of dehydration, oliguria or hypotension. Fluid accumulation is due to increased capillary permeability rather than hypoalbuminemia or cardiac, hepatic or renal damage. It is slowly reversible after treatment is discontinued (median 29 [range, 0 to > 42] weeks). However, early, aggressive diuretic treatment may occasionally be required. Antihistamines have not been shown to be useful in controlling fluid retention.

Neuropathy: Rarely, neurologic effects result in moderate to severe neuropathy, leading to decreased dexterity and/or disturbances in gait, usually after cumulative doses of 600 mg/m^2.

Alopecia: Loss of hair, including on the head, eyebrows, eyelashes, pubic area, and underarm, occurs in most patients. Alopecia has a sudden onset, and occurs 14-21 days after treatment has begun. Hair should grow back once treatment has been completed; however cases of poor hair regrowth and/or persistent hair loss have been reported. Reports suggest some patients may experience prolonged hair loss lasting beyond 24 months, and possibly irreversibly.

Rash/pruritus: Cutaneous reactions are characterized by a rash, including localized eruptions mainly on feet and hands, but also on arms, face or thorax. These reactions are observed in 48% of patients. They are occasionally associated with pruritus. Eruptions generally occur within one week following the docetaxel infusion, resolve before the next infusion, and are not disabling.

Injection site reactions include skin sensitivities such as hyperpigmentation, inflammation, local erythema, dryness of the skin, or swelling of the vein. Injection site reactions occur in 6% of patient and are generally mild. Phlebitis or extravasations are observed less frequently. Leakage into surrounding tissue during intravenous administration (i.e., extravasation) may cause irritation, local tissue necrosis and/or thrombophlebitis.

Nail changes are characterized by hyperpigmentation, splinter hemorrhage, subungual hematoma and hyperkeratosis, orange discoloration, Beau-Reil lines (which indicate the cessation of nail growth), and acute paronychia. Some changes are cosmetic and asymptomatic, whereas others can be accompanied by discomfort or pain. Changes are usually transient and disappear with treatment withdrawal, although there are reports of persistent changes. Loosening or loss of nails (onycholysis) occurs in 2-22%. Nail bed infections may be a complication and the application of topical antibiotics or antifungals may be necessary. Applying the principle of cold-induced vasoconstriction by wearing frozen gloves on the hands during treatment may reduce the incidence of nail and skin toxicity. In one study, overall incidence of nail toxicity was reduced with frozen glove treatment from 51% to 11%, and the incidence of grade 2 toxicity (onycholysis) was reduced from 22% to 0%. Additionally, median time of occurrence of nail toxicity was delayed to 106 days with frozen glove treatment as opposed to 58 days without.

Hand-foot skin reaction that occurs despite dexamethasone prophylaxis may respond to administration of pyridoxine 50 mg orally three times a day.

Weekly schedule toxicity profile: The toxicity profile of docetaxel is markedly altered when the drug is administered on a weekly schedule. Myelosuppression, a severe and dose-limiting toxicity of the 3 weekly schedule, is not usually a clinically important problem when docetaxel is administered weekly. At the maximum tolerated dose of 43 mg/m²/week (equivalent in dose intensity to 129 mg/m² every 3 weeks), grade 3 leukopenia occurs in 14% of courses, with no grade 4 leukopenia. With this dosing schedule, fatigue and asthenia are the dose-limiting toxicities.

Tearing/watery eyes: An unexpected toxicity with the weekly schedule is excessive tearing, which was reported by half of the patients in a phase II study in women with metastatic breast cancer. Patients reported increased tearing and, in some cases, mild conjunctivitis or eye irritation. Formal ophthalmologic examination of several patients revealed no abnormalities. As with fluid retention, the onset of tearing seems to be related to cumulative dose and occurs after a median of 400 mg/m² (range, 120-960 mg/m²). Ten of 15 patients with tearing also developed some degree of fluid retention. Treatment with artificial tears or other ocular moisturizers ameliorated symptoms in some patients. Eye irritation led to a dose reduction in one patient.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dexamethasone	does not affect protein binding of docetaxel		
doxorubicin	AUC of docetaxel increased, one hour interval between drugs does not change the results	doxorubicin may interfere at hepatic microsomal enzyme level	avoid concurrent therapy outside of clinical trial
epirubicin	increased exposure to active metabolite of epirubicin	altered metabolism of epirubicin	avoid concurrent therapy outside of clinical trial
etoposide	clearance of docetaxel decreased		avoid concurrent therapy outside of clinical trial
ifosfamide	when docetaxel given first it is associated with increased ifosfamide plasma clearance and decreased AUC	may be due to increased ifosfamide metabolism caused by corticosteroid premedication for docetaxel	avoid concurrent therapy outside of clinical trial

Table 11

There have been no formal clinical studies to evaluate the drug interactions of docetaxel with other medications. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolized by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as cyclosporine, ketoconazole and erythromycin.

DOSAGE GUIDELINES:

PLATELET COUNT ($\times 10^9$/L)	ABSOLUTE NEUTROPHIL (ANC)* ($\times 10^9$/L)			
	$\geq$ 1.8	1.5-1.8	1.0-1.5	<1.0
$\geq$ 100	100%	75%	50%	0%
70-100	75%	75%	50%	0%
50-70	50%	50%	50%	0%
<50	0%	0%	0%	0%

Table 12

* ANC = WBC x (% polys + % stabs)

** 0% Indicates treatment should be postponed a week until the counts return to a level at which drugs may be given.

Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities. [49]

Dosage in hepatic failure*:

Cycle length	**Alkaline** *Phosphatase*		**AST +/or ALT**	**Dose**
3 weeks:	< 2.5 x ULN	and	<1.5 x ULN	100%
	2.5 – 5 x ULN	and	1.6 – 5 x ULN	75%
	> 5 x ULN	or	> 5 ULN	discuss with contact physician

Cycle length	**AST**	**Dose**
8 weeks:	< 1.5 x ULN	100%
	> 1.5 x ULN	delay until levels have subsided, then restart at a 75% dose

Table 13

*Liver enzymes are recommended before cycle 1 and then prior to each treatment if clinically indicated (e.g., if liver enzymes are elevated, liver metastases are present or there is severe toxicity such as neutropenia). If liver enzymes are normal and there is no evidence of liver metastases or severe toxicity, check liver enzymes after 3 cycles (ie, at cycle 4).

Dosage in severe peripheral neuropathy:	Cycle length 3 weeks:	reduce by 25% to 75 mg/m2; further reduce by 25% to 55 mg/m2 if reactions continue; discontinue if patient experiences ≥ grade 3 peripheral neuropathy3
Dosage in severe or cumulative cutaneous reactions:	Cycle length 3 weeks:	reduce by 25% to 75 mg/m2; further reduce by 25% to 55 mg/m2 if reactions continue

Table 14

Dosage in dialysis: Hemodialysis: no significant removal; no dose adjustment required, may be administered before or after hemodialysis.

9.1.4 Abraxane

DRUG NAME: Paclitaxel, nanoparticle, albumin-bound (nab)

SYNONYM(S): **protein-bound paclitaxel**

COMMON TRADE NAME(S): **ABRAXANE®**

CLASSIFICATION: **antimicrotubule agent**

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Paclitaxel, the active ingredient of nanoparticle, albumin-bound (nab) paclitaxel, is an antimicrotubule agent that promotes the assembly and stabilization of microtubules, thus inhibiting normal dynamic reorganization of the microtubule network. Paclitaxel induces abnormal bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. It is thought that albumin-bound paclitaxel (nab-paclitaxel) facilitates the transport of paclitaxel across the endothelial cell via an albumin-receptor mediated pathway. Nab-paclitaxel is cell cycle phase-nonspecific. [50]

PHARMACOKINETICS:

Distribution	extensive extravascular distribution and tissue binding

	cross blood brain barrier?	no information found
	volume of distribution	632 L/m2
	plasma protein binding	89-98%
Metabolism	extensive; primarily via CYP 2C8, minor metabolites via CYP 3A4	
	active metabolite(s)	6α-hydroxypaclitaxel (major), 3'-*p*-hydroxypaclitaxel (minor), and 6α,3'-*p*-dihydroxypaclitaxel (minor)
	inactive metabolite(s)	no information found
Excretion	extensive non-renal clearance	
	urine	4% (unchanged drug); <1% (6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel)
	feces	20%
	terminal half life	27 h
	clearance	15 L/h/m2

Table 15

USES: Primary uses: * Breast cancer
SPECIAL PRECAUTIONS:
Caution: nab-paclitaxel is **NOT interchangeable** with other paclitaxel formulations and should not be substituted. nab-paclitaxel has not been studied in patients previously exhibiting hypersensitivity to paclitaxel or human albumin, routine premedication to prevent hypersensitivity reactions is not required before administration. nab-paclitaxel contains albumin which, although no cases have been identified, carries a remote risk for transmission of viral diseases.
Mutagenicity: not mutagenic in Ames test and mammalian in vitro mutation test. Paclitaxel is clastogenic in mammalian in vitro and in vivo chromosome tests.
Fertility: In animal studies with paclitaxel, testicular atrophy/degeneration in males, as well as significantly reduced fertility, decreased pregnancy rates and increased loss of embryos in untreated female mates have been observed. Skeletal and soft tissue fetal anomalies were also observed. Men are advised not to father a child while receiving treatment with nab-paclitaxel.
Pregnancy: FDA Pregnancy Category D. In animal studies, paclitaxel has demonstrated embryo- and fetotoxicity, including fetal anomalies and intrauterine mortality. No studies have been conducted in women. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Breastfeeding is not recommended due to the potential secretion into breast milk. Concentrations in milk were detectable in animal studies.
SIDE EFFECTS:
The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	**SIDE EFFECT**
blood and lymphatic system/ febrile neutropenia	**anemia** (20-33%, severe 1%); sometimes requiring blood transfusion
	bleeding (2%)
	febrile neutropenia (2%)
	leucopenia (72%)
	neutropenia (80%, severe 9%); dose-limiting; see paragraph following **Side Effects** table
	thrombocytopenia (2%, severe <1%); may require dose reduction
cardiac	**bradycardia** (<1%); usually asymptomatic, intervention not required

	cardiovascular events (3%), including cardiac arrest, chest pain, edema, hypertension, pulmonary emboli, supraventricular tachycardia, and thrombosis
	hypotension (5%); usually asymptomatic, intervention not required
eye (see paragraph following **Side Effects** table)	blurred vision (1%)
	keratitis (1%)3
gastrointestinal	emetogenic potential: low
	anorexia (>10%)
	constipation (>10%)
	diarrhea (27%, severe <1%)
	mucositis (7%, severe <1%); occurs a few days post treatment, usually decreases or disappears within 1 week **nausea** (30%, severe 3%) **vomiting** (18%, severe 4%)
general disorders and administration site conditions	extravasation hazard: irritant.
immune system	fever (14%)
	fluid retention/edema (10%)
	injection site reactions (1%); usually mild; rarely has included phlebitis, cellulitis, induration, exfoliation, necrosis, and fibrosis
	hypersensitivity reactions (4%); see paragraph following **Side Effects** table
infections and infestations	**infections** (24%, severe 3%); oral candidiasis, pneumonia, and respiratory tract infections most frequently reported
investigations	alkaline phosphatase increase (36%)
metabolism and nutrition	AST increase (39%)
	bilirubin increase (7%)
	ECG abnormalities (60%, 35% in patients with normal baseline); usually asymptomatic; not dose-limiting, intervention not required
	gamma-glutamyltransferase increase (50%, severe 3-14%)
	serum creatinine increase (11%, severe <1%); dose reductions or delays not required
	dehydration (1-10%)
musculoskeletal and connective tissue	**arthralgia/myalgia** (44%, severe 8%); occurs two to three days post treatment, usually transient
nervous system	**asthenia** (47%, severe 8%), including fatigue, weakness, lethargy, and malaise; may affect ability to drive and operate machines
	sensory neuropathy (71%, severe 10%); may require dose reduction; see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (6-7%)6
skin and subcutaneous tissue	**dyspnea** (12%)
	pneumothorax6 (<1%)
	pulmonary embolism
	alopecia (90%)
vascular	nail changes (1%); includes changes in pigmentation or discoloration of nail bed
	pruritus (6%)
	rash (9%)
	flushing (2%)

Table 16

Bone marrow suppression, primarily neutropenia, is a dose-dependent and dose-limiting toxicity. Neutropenia is usually rapidly reversible. Frequent blood count monitoring is recommended, and treatment should not be initiated if baseline neutrophil counts are less than 1.5 x 109/L. Dose reduction is recommended for severe neutropenia lasting one week or longer and further reduction is recommended for recurrence of the same.

Hypersensitivity reactions are reported in 4%, with none reported as severe. On the day of dosing, grades 1 and 2 dyspnea are reported in 1%, and flushing, hypotension, chest pain, and arrhythmia are reported in less than 1%

each. Nab-paclitaxel has not been studied in patients previously exhibiting hypersensitivity to paclitaxel or human albumin.

Neurologic toxicity is dose-dependent and is influenced by prior and/or concomitant therapy with neurotoxic agents. In clinical trials, the frequency of sensory neuropathy increased with cumulative dose, and sometimes required discontinuation of treatment. It is suggested that grade 3 sensory neuropathy requires treatment interruption until resolution, followed by dose reduction for subsequent courses. Severe sensory symptoms typically improved a median of 22 days after treatment interruption. Cases of autonomic neuropathy resulting in paralytic ileus have been reported. Ischemic stroke, metabolic encephalopathy, confusion, dizziness/lightheadedness, and mood alteration/depression are neurologic events reported in less than 1%.

Ocular/visual disturbances have been reported in 13%, with 1% of cases reported as severe. The severe cases (keratitis and blurred vision) were reported in patients receiving doses higher than recommended, and were usually reversible. Rarely, persistent optic nerve damage has been reported. [50]

INTERACTIONS:

Drug interaction studies have not been conducted. However, nab-paclitaxel is a substrate of CYP 2C8 and 3A4 and caution should be exercised during concurrent therapy with known inhibitors or inducers of these enzymes. The clinical significance of these interactions is unknown.

DOSAGE GUIDELINES:

PLATELET COUNT ($\times 10^9$/L)	ABSOLUTE NEUTROPHIL (ANC)* ($\times 10^9$/L)			Table 17
	≥ 1.8	1.5-1.8	1.0-1.5	<1.0
≥ 100	100%	75%	50%	0%
70-100	75%	75%	50%	0%
50-70	50%	50%	50%	0%
<50	0%	0%	0%	0%

* ANC = WBC x (% polys + % stabs)
** 0% Indicates treatment should be postponed a week until the counts return to a level at which drugs may be given.

Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities. [50]

	AST	**Serum bilirubin**	**Dose**	
mild	< 10xULN	≤ 1.25xULN	260 mg/m2 (100%)	
moderate	< 10xULN	1.26-2xULN	reduce to 200 mg/m2 *	
severe	< 10xULN	2.01-5xULN	reduce to 130 mg/m2 **	
	> 10xULN	> 5xULN	not recommended	Table 17a

***** For subsequent cycles: dosing based on patient tolerability.
****** For subsequent cycles: may consider dose escalation to 200 mg/m2 based on patient tolerability.

9.1.5 Ixabepilone

DRUG NAME: Ixabepilone
SYNONYM(S):
COMMON TRADE NAME(S): **IXEMPRA®**
CLASSIFICATION: **miscellaneous, antineoplastic**

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.
MECHANISM OF ACTION:
Ixabepilone is a semi-synthetic analog of epothilone B that binds to beta-tubulin subunits on microtubules, leading to suppression of microtubule dynamics; specifically, the dynamic instability of alpha-beta-II and alpha-beta-III microtubules, which leads to apoptosis. Ixabepilone is cell cycle phase-specific. [51]
USES: Primary uses: Breast cancer
SPECIAL PRECAUTIONS:
Caution: premedication with H1 and H2 antagonists is recommended dosage adjustment may be necessary for hepatic dysfunction and for concomitant use with strong CYP 3A4 inhibitors
Fertility: impaired fertility in animal studies
Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk(e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Breastfeeding is not recommended due to potential secretion into breast milk.
SIDE EFFECTS:
The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	**SIDE EFFECT**
allergy/immunology	**hypersensitivity reactions (5%)**
auditory/hearing	vertigo (4%)
blood/bone marrow/ febrile neutropenia	anemia (6%) **leukopenia (36%)** **neutropenia (23%)** thrombocytopenia (2%)
cardiovascular (general)	myocardial ischemia (2%)
constitutional symptoms	fatigue (56%)
	hot flush (6%)
dermatology/skin	extravasation hazard: none
	alopecia (48%)
	nail disorder (9%)
	palmar-plantar erythrodysesthesia (8%)
	pruritis (6%)
	skin rash (9%)
gastrointestinal	emetogenic potential: low
	abdominal pain (13%)
	anorexia (19%)
	diarrhea (22%)
	nausea (42%)
	stomatitis/mucositis (29%)
hepatobiliary/pancreas	acute hepatic failure, jaundice
infection	upper respiratory tract infection (6%)
musculoskeletal	myalgia/arthralgia (49%)
neurology	headaches (11%)
	peripheral neuropathy (62%)
ocular/visual	lacrimation increased (4%)
pain	musculoskeletal pain (20%)
	pain (8%)

pulmonary	cough (2%)	Table 18
	dyspnea (9%)	

DOSAGE GUIDELINES:

PLATELET COUNT (x 10^9/L)	ABSOLUTE NEUTROPHIL (ANC)* (x 10^9/L)			Table 19
	≥ 1.8	1.5-1.8	1.0-1.5	<1.0
≥ 100	100%	75%	50%	0%
70-100	75%	75%	50%	0%
50-70	50%	50%	50%	0%
<50	0%	0%	0%	0%

* ANC = WBC x (% polys + % stabs)
** 0% Indicates treatment should be postponed a week until the counts return to a level at which drugs may be given.

Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities. [51]

9.2 Discontinuation of Subjects from Treatment:

Subjects MUST discontinue study treatment (investigational or non-investigational treatment) for any of the following reasons:

• Withdrawal of informed consent (subject's decision to withdraw for any reason).
• Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
• Pregnancy.
• Termination of the study by the sponsor, by the local IRB or by the supporting/funding organization (The Methodist Hospital Cancer Center)
• Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

All subjects who discontinue study treatment should comply with protocol-specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

10.0 CRITERIA FOR RESPONSE

Tumor Assessment by RECIST 1.1

Tumor assessments will be made by the investigator according to RECIST 1.1.

10.1. Definition of Target and Non-target Lesions According to RECIST 1.1

Numbers will be assigned to the lesions chosen as target and non-target. These assigned numbers must remain the same throughout the study. Lesion numbers should be recorded in the radiology report and transcribed to the CRF. To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Measurable disease is defined by the presence of at least one measurable lesion.

At baseline, tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10mm by CT scan. At baseline, lesions will be categorized as follows:

10.1.1. Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and

measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected.
A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. Target lesion criteria are listed for CR, PR, stable disease (SD), and PD in Table 20.

10.1.2. Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.
Non-target lesion criteria are listed for CR, Non-CR/Non-PD, and PD in Table 21.

Target Lesion Response Criteria

Response Category	Criteria
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Table 20

Non-target Lesion Response Criteria

Response Category	Criteria
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level1 (if present). All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of 1 or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits (if present)
Progressive Disease (PD)	Appearance of 1 or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Table 21

11 Study Materials:

11.1 Chloroquine

DOSAGE AND ADMINISTRATION

The dosage of chloroquine phosphate is often expressed in terms of equivalent chloroquine base. Each 500 mg tablet of ARALEN contains the equivalent of 300 mg chloroquine base.

HOW SUPPLIED

Tablets containing 500 mg chloroquine phosphate USP, equivalent to 300 mg of chloroquine base, bottles of 25 (NDC 0024-0084-01).

White, film-coated convex, discoid tablet, 1/2 inch in diameter with an uncoated core, printed in black ink with a stylized "W" on one side and an "A77" on the other side.

Dispense in tight, light-resistant container as defined in the USP/NF. [47]

Store at 25° C (77° F); excursions permitted to 15° – 30° C (59° – 86° F) [see USP Controlled Room Temperature]

11.2. Paclitaxel

SUPPLY AND STORAGE:

Injection: Biolyse Pharma supplies paclitaxel as a 6 mg/mL preservative-free solution in single-dose vials of 5 mL, 16.7 mL and 50 mL. Non-medicinal ingredients: dehydrated ethanol 49.7% and Cremophor EL (polyethoxyethylated castor oil). Refrigeration is recommended for long term storage. The potency of paclitaxel is not affected when transported or stored for up to two months at room temperature. Protect vials from light (keep intact vials in their container until use). Discard unused portion within 8 hours after puncture. Bristol-Myers Squibb supplies paclitaxel as a 6 mg/mL preservative-free solution in multidose vials of 5 mL, 16.7 mL and 50 mL. Non-medicinal ingredients: dehydrated ethanol 49.7% and Cremophor EL (polyethoxylated castor oil) 527 mg. Store vials at room temperature and protect from light (keep intact vials in their container until use). Both the 5 mL vial and the 16.7 mL vial are stable for 48 hours at room temperature after puncture. The 50 mL vial is stable for 24 hours at room temperature after puncture. [48]

SOLUTION PREPARATION AND COMPATIBILITY:

Additional information: Non-polyvinyl (non-PVC) equipment (e.g., polyethylene) is used to minimize leaching. The surfactant, Cremophor EL (polyoxyethylated castor oil), leaches the plasticizer, diethylhexyl phthalate (DEHP), from polyvinyl chloride (PVC) bags and administration sets. Actual hazardous exposure levels to DEHP are not known; however, it is hepatotoxic and exposure should be minimized. Use of a plastic syringe to measure a dose is acceptable but drug-syringe contact time should be minimized.

Bacterial challenge: Paclitaxel (Bristol) 0.7 mg/mL diluted in NS did not exhibit an antimicrobial effect on the growth of three of four organisms inoculated into the solution. Microbiological growth should be considered when assigning expiration periods.

Compatibility: The following are compatible with paclitaxel **via Y-site injection**: acyclovir, amikacina, aminophylline, ampicillin, bleomycin, butorphanol, calcium, carboplatin, cefepime, cefotetan, ceftazidime, ceftriaxone, cimetidine, cisplatin, cladribinea, cyclophosphamide, cytarabinea, dacarbazine, dexamethasone, diphenhydramine, doxorubicin, droperidol, etoposide, etoposide phosphate, famotidine, floxuridine, fluconazole, fluorouracil, furosemide, ganciclovir, gatifloxacina, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone, hydromorphone, ifosfamide, linezolid, lorazepam, magnesium, mannitol, meperidine, mesna, methotrexate, metoclopramide, morphine, nalbuphine, ondansetron, pentostatin, potassium, prochlorperazine, propofol, ranitidine, sodium bicarbonate, thiotepa, topotecan, certain TPN formulations, vancomycin, vinblastine, vincristine, zidovudine. The following are compatible with paclitaxel **in the same infusion solution** at certain concentrations and diluents: carboplatin, cisplatin, doxorubicin. **Incompatibility:** The following are incompatible with paclitaxel **via Y-site injection**: amphotericin B, amphotericin B cholesteryl

sulphate complex, chlorpromazine, doxorubicin liposomal, hydroxyzine, methylprednisolone, mitoxantrone. [48]

PARENTERAL ADMINISTRATION:

Intermittent infusion	**in appropriate volume of NS** or D5W **over 1-3 h** (range 1-24 h) dilute in non-PVC bags dilute to final concentration of 0.3-1.2 mg/mL premedication required to prevent hypersensitivity reactions administer through non-PVC tubing and a 0.22 micron (non-PVC) in-line filter equipment Table 22
Continuous infusion	**as for intermittent infusion except given over 24 h**

11.3. TAXOTERE

SUPPLY AND STORAGE:

Injection: sanofi-aventis supplies concentrated drug solution in 20 mg/0.5 mL and 80 mg/2 mL vials and diluent in 1.5 mL and 6 mL vials. Concentrated drug solution vials contain polysorbate 80; diluent vials contain ethanol 95%. Refrigerate. Protect from bright light.

SOLUTION PREPARATION AND COMPATIBILITY:

Additional information: Both docetaxel and diluent vials contain overfill to ensure that the extractable volume of premixed docetaxel solution corresponds to the labeled amount. The combined solution of concentrate and supplied diluent should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the combined solution to stand for 5 minutes to allow foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

Contact of the concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solution for infusion is not recommended. To minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, docetaxel infusion solution should be stored in bottles (e.g., glass, polypropylene) or non-PVC plastic bags (e.g., polypropylene, polyolefin), and administered through non-PVC or polyethylene-lined administration sets. [49]

PARENTERAL ADMINISTRATION:	
Direct intravenous	not recommended, due to need to initiate injection slowly to reduce the risk of allergic reactions
Intermittent infusion	***in 250 mL NS over 1 h (use non-PVC equipment)*** Patient must have received a minimum of 3 doses of dexamethasone before each treatment. slow initiation of infusion is not routinely needed to reduce the risk of allergic reactions if slow initiation of infusion is needed, start infusion at 30 mL/h x 5 min, then 60 mL/h x 5 min, then 120 mL/h x 5 min, then complete infusion at 250 mL/h (for 500 mL bag, continue 250 mL/h for 5 min and then complete infusion at 500 mL/h) Observe patient constantly for signs of hypersensitivity during the first 10-15 min of the infusion. A volumetric cassette infusion pump may be used to ensure that the docetaxel is infused at a consistent and accurate rate. A pump is not mandatory, but is suggested if the IV cannot be monitored closely so that it is on time. Table 23

11.4. ABRAXANE

SUPPLY AND STORAGE:

Injection: Abraxis BioScience Canada, Inc. supplies nanoparticle, albumin-bound (nab) paclitaxel in single use vials of sterile lyophilized powder containing 100 mg of paclitaxel and 900 mg of human albumin. Store at room temperature. Protect from light.

SOLUTION PREPARATION AND COMPATIBILITY:

Additional information: Gently swirl or slowly invert vial after reconstitution to avoid foaming. If foaming or clumping occurs, stand solution for a minimum 15 minutes until foaming subsides.

Reconstituted product should be milky and homogeneous without visible particulates. Some settling may occur upon standing and vial should be gently inverted to ensure complete resuspension prior to use. Product must be discarded if precipitates are observed. Neither freezing nor refrigeration adversely affects stability of the product. [50]

PARENTERAL ADMINISTRATION:

Intermittent infusion	**Over 30 minutes*, do** NOT filter; Non-PVC bags and tubing are NOT required.

* Limiting infusion time to 30 minutes reduces the likelihood of infusion-related reactions.

11.5. IXABEPILONE

SUPPLY AND STORAGE:

Injection: Bristol-Myers Squibb supplies ixabepilone as a kit containing a 15 mg or 45 mg vial of ixabepilone for injection together with an 8 mL or 23.5 mL vial of supplied diluent which both provide ixabepilone 2 mg/mL solution after reconstitution. Refrigerate. Retain in original package until time of use.

Additional information: Administer using an in-line filter with a microporous membrane of 0.2 to 1.2 microns. Non-PVC (i.e., DEHP-free) infusion containers and administration sets must be used. [51]

PARENTERAL ADMINISTRATION: Intermittent infusion **over 3 hours.**

12. Investigational Product Records at Investigational Site(s)

The study drug will be kept in the investigational pharmacy at the sponsor site The Methodist Hospital Cancer Center (TMHCC). It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount destroyed at study site.

13. Destruction of Investigational Product

N/A

Drug Ordering and Accountability

The Methodist Hospital Cancer Center (TMHCC) will assume all the cost related with the Chloroquine tablets during the length of the study.

Initial Orders

Following submission and approval of the required regulatory documents, the TMHCC will supply the participating patient (s) with an initial dose of Chloroquine.

Re-supply

Re-supply of chloroquine will be provided accordingly with the number of patients enrolled in the trial. The research coordinator will ensure that enough study drug is kept in the investigational pharmacy at all times.

14. Study Discontinuation

Participants developing toxicities of any grade will be permitted to take a drug holiday of up to five (5) days. After the drug holiday, if the adverse event has resolved to the satisfaction of the investigator, the study medication may be resumed. If the adverse event recurs, the participant may be taken off study at the discretion of their physician. NOTE: Patients who develop any of the following adverse events must be permanently discontinued from study:
A patient will be considered to have withdrawn from investigational treatment if the principle reason for ending treatment falls into 1 of the following categories:

- Unacceptable toxicity, as defined by the study protocol and/or at the discretion of the principle investigator.
- Insufficient therapeutic effect (lack of efficacy/progressive disease), at any timepoint throughout the study.
- Non-compliance with protocol, as defined by a pill count of less than 75% on more than one occasion.
- Lost to follow-up.
- Pregnancy.
- Withdrawal of consent.

14.1 Withdrawal Procedures

Treatment with investigational drugs must be stopped at the time of investigational treatment discontinuation. The patient will be asked to return to the clinic with all unused study drug and to see their study doctor if they are discontinued from the study. If the subject agrees, an exit biopsy will be performed at this time. The study doctor will examine the subject and the subject will be discontinued from the trial. The reason for discontinuation will be clearly documented in the subject's medical records and recorded on the CRF. Subjects will be followed for safety as described in section 15.1.3.
All data up to the time of withdrawal/discontinuation will be included in the analyses.

14.2 Lack of Efficacy

The investigational therapeutic regimen will be discontinued immediately if at any timepoint the patient shows signs of disease progression. Patients who are discontinued prematurely due to disease progression will be switched to standard of care therapy chosen by the treating physician.

15. Adverse Events

15.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse. Anticipated day-to-day fluctuations of the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered an adverse event. All adverse events occurring from the first dose of investigational product until thirty days after the last dose must be reported regardless of whether or not they are considered drug related. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

It is the responsibility of the IND holder to comply with IND safety reporting as set forth in the Code of Federal Regulations, Section 312.32.
A serious AE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization,
  NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency room for observation and/or treatment that would have not been appropriate in the physician's office or outpatient setting. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is NOT considered an AE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- results in the development of drug dependency or drug abuse
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Also is considered the occurrences of pregnancy or overdose (regardless of adverse outcome), and cancer as events which must be reported as important medical events.

15.1.1 Reporting of SAEs

Following the subject's written consent to participate in the study, all SAEs should be collected and reported, including those thought to be associated with clinical trial procedures. All serious adverse events must be reported to the FDA, the coordinating center, and The Methodist Hospital Research Institute by the investigator.
SAE terminology and severity grading will be based on (CTCAEv4).
The following categories and definitions of causal relationship to study drug should be considered for use for this clinical study.

- Certain: There is a known causal relationship between the study drug and the SAE. The event responds to withdrawal of study drug (dechallenge), and recurs with rechallenge when clinically feasible. (>95% certainty)
- Probable: There is reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge. Rechallenge is not required. (65%-95% probability)
- Possible: There is reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear. (35%-65% probability of relatedness)
- Not likely: There is temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the SAE. (5-35% probability of relatedness)
- Not related: There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is known causal relationship between the SAE and another drug, concurrent disease, or other circumstance. (<5% chance of relatedness)
- Adverse events classified as "serious" require expeditious handling and reporting to the sponsor The Methodist Hospital Cancer Center (TMHCC) and local IRB to comply with regulatory requirements.

- All serious AEs whether related or unrelated to chloroquine must be immediately reported to the coordinating site (TMHCC) by the investigator or designee within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.
  All SAEs should be faxed or emailed to

  The Methodist Hospital Cancer Center at:
  Afroehlich@tmhs.org
  Fax Number: 713-793-1642
- For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information.

- The Methodist Hospital Cancer Center will be provided with a simultaneous copy via facsimile of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, which can be accessed at:
  http://www.accessdata.fda.gov/scripts/MedWatch/
  MedWatch forms should be sent to the FDA at:

  MEDWATCH
  5600 Fishers Lane
  Rockville, MD 20852-9787
  Fax: 1-800-FDA-0178 (1-800-332-0178)

  - Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed by the sponsor. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.
  - An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, the sponsor considers an overdose, regardless of adverse outcome, as an important medical event.
  - AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of chloroquine or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post-treatment follow-up as appropriate.

15.1.2 Reporting SAEs "Pregnancy"

A subject who has a positive serum β-HCG pregnancy test result at any time after the first dose of investigational therapy will be immediately withdrawn from participation in the study. All study conclusion/withdrawal assessments will be collected at the time of discontinuation as described in section 14.1
The investigator will collect pregnancy information on any female patient who becomes pregnant during study participation. The investigator will record pregnancy information on the appropriate form and submit it to TMHRI within 2 weeks of learning of a patient's pregnancy. Information on the status of the mother and child will be forwarded to TMHRI. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of pregnancy will be reported. The time period for collecting pregnancy information

is identical to the time period for collecting AEs. Pregnancy information is collected from the first dose of investigational product to 30 days after the last dose.
While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.
A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the investigational product(s) by the investigator, will be reported to TMHRI.

15.1.3 Follow-up Adverse Events

Investigators should follow-up subjects with adverse events until the event has subsided (disappeared) or until the condition has stabilized. Subjects will be followed for adverse events and serious adverse events for 30-days from the last dose of study drug. During the 30-day follow-up period, new onset adverse events should only be recorded if, in the opinion of the investigator, there is a possibility the event is attributable to the investigational product. Adverse events that are clearly related to the next phase of the patient's treatment (e.g. alopecia in a patient receiving chemotherapy) should NOT be recorded.

15.2 Reporting of Results to Subjects and their Physicians

The results of the immunohistochemical staining are purely investigational and thus will not be reported back to the patient or their physician. As the biomarker analyses will be done in batches, the results may not be available for many months after the tissue sampling is done.

16. Data Management

TMHRI utilizes Velos eResearch, a web-based Clinical Trial Management System. Reusable system components allow patient information to be tracked and managed on an organization, disease and department specific basis. Researchers use Velos eResearch Patient Profiling to screen patients, track clinical outcomes, and introduce routine clinical data capture, management and research practices in their organizations. Velos eResearch provides full Electronic Data Capture (EDC) compliant with HIPAA and 21 CFR Part 11 regulations. Custom-built case report forms allow data capture over the web from any study site. A robust data query engine enables granular data and study queries across multiple forms, patients, and studies. eResearch was originally designed for use at Cancer Centers, and incorporates standard NCI reports in the application. Velos eResearch is powered by an Oracle database engine. The configuration at TMHRI will be adequate to handle the data generated from these projects. All patients who received any amount of study drug will be included in the safety analysis. Subjects will be monitored at each clinic visit and at any contact with the subject throughout the study for the occurrence of AEs and SAEs. The investigator or site staff will inquire about the occurrence of AEs/SAEs at every clinic visit or contact during the study. Adverse events will be graded according to the NCI Common Terminology Criteria v. 4.0. All AEs that occur during active treatment will be recorded in subject source documents and on CRFs, regardless of grade or relationship to investigational treatment. Non-serious adverse events that occur within the 30 day follow-up period will only be recorded on the CRFs if the investigator believes there to be a possible relationship to study medication. Serious adverse events should be recorded, regardless of relationship to drug.
Safety analyses will include summaries of adverse event rates (both frequency and incidence tables), baseline laboratory parameters and changes from baseline, frequency of CTC toxicity grades for both laboratory and non-laboratory data.
During the clinical trial, clinical data on all participants enrolled on the study will be reviewed in our Data and Safety Monitoring Committee meeting and monthly in Cancer Center Clinical Research Data Review meeting.

17. Statistical Design and Analyses

A sample size of 47 patients achieves 80% power to detect the difference between the null median overall response rate (ORR) of 30% and the alternative hypothesis median ORR 50% at a 0.05 significance level (alpha) using a two-sided binomial test.

18. RESPONSIBI L I T I ES

18.1. Investigator Responsibilities

18.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in full compliance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subjects. The investigator will ensure that the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, Responsibilities of Sponsor and Investigators, 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. Since this is a covered clinical trial, the investigator will ensure that 21 CFR, part 54, 1998, is adhered to; a covered clinical trial is any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety. This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the Sponsor or proprietary interests in the drug being studied. This documentation must be provided prior to the participation of the investigator and any sub-investigator. The investigator and sub investigator agree to notify the Sponsor of any change in reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

18.1.2. Institutional Review Board or Independent Ethics.

Committee Prior to initiation of the study, the study protocol will be submitted with its associated documents (e.g., Schedule of Assessments, Subject Information and Consent Forms, Investigator's brochure) to the relevant Institutional Review Board (IRB) or independent Ethics Committee (IEC) for approval. The approval of the relevant IRB/IEC will be filed in the Investigator Site File and a copy will be kept in the Study Master Files. The study will only commence following a written approval. Documentation of the date of the IRB/IEC meeting, constitution of the committee and voting members present at the meeting, and a statement confirming that the IRB/IECs operate in accord with GCP will be requested by the Sponsor. The Sponsor also requires written evidence that clearly identifies the study number, clinical study protocol version, informed consent documents, and Investigator's Brochure Version reviewed. Any amendments to the protocol will be submitted to the relevant IRB/IEC for approval and the IRB/IEC will be informed about SAEs in accordance with local and national requirements. Amendments may only be implemented after approval by the IRB/IEC and submission to the appropriate regulatory authority unless required to eliminate an immediate safety risk to the subject. Regulatory Authority approvals/authorizations/notifications, where required must be in place and fully documented prior to trial start.

18.1.3. Subject Information and Informed Consent

Written informed consent must be obtained from the subject prior to study participation. The informed consent document must be signed and dated by the subject and properly witnessed before initiation of any study procedures including any change in medication or initiation of study drug dosing. Subjects must be consented in accordance with all local regulatory and legal

requirements. This process must include a verbal explanation of the nature, scope, and possible consequences of the study provided in plain language. The information should be presented by the investigator unless a designee is permitted by local regulations. The potential study subject should be encouraged to ask questions about the study. The informed consent document must be prepared in accordance with GCP guidelines and with local regulatory and legal requirements. A copy of the signed consent form will be given to the subject and the original document must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. The site will retain the original signed/dated consent form and any associated HIPAA authorization, if applicable for all consented subject candidates. If applicable, the document will also be provided in a certified translation of the local language. The informed consent will be updated as appropriate (e.g., due to protocol amendment or if significant new safety information that may be relevant to consent of the subjects becomes available). If the informed consent ids revised, it is investigator responsibility to ensure that an amended consent form is reviewed and signed by all subjects subsequently entered into the study and those currently in the study.

18.1.4. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. Subject names will not be supplied to the sponsor. Only the subject number and subject identifier will be recorded in the case report form, and if the subject name appears on any other document (e.g., pathologist report), it must be de-identified before a copy of the document is supplied to the sponsor. The investigator must assure that subject's anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials and an identification code (i.e., not names) should be recorded on any form submitted to the sponsor and IRB. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. The subjects will be informed in writing that representatives of the sponsor, IRB/IEC, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection laws.

18.1.5. Study Files and Retention of Records.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories (although not limited to) the
Following: (1) investigator's study file, and (2) subject clinical source documents. It is the responsibility of the investigator to ensure that the study center file is maintained in accord with Section 8 of the ICH GCP Guidelines. The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence. Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include (although not limited to) the following: subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, CT MRI scan, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.
All clinical study documents must be retained by the investigator until at least two years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not

approved for such indication, until two years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements or an agreement with Abbott. The investigator must notify Abbott prior to destroying any clinical study records. Should the investigator wish to assign the study records to another party or move them to another location, Abbott must be notified in advance. If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Abbott to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the Subject, appropriate copies should be made for storage outside of the site.

19. CONSENT PROCEDURES

Written informed consent will be obtained from all participants by the investigators or their designee. The investigator or his/her designee will introduce the study, assist in obtaining the signed informed consent, and provide the participant with a copy of the signed consent form. A signed, written informed consent must be obtained prior to performing any study specific procedures or assessments.

19.1 CONFIDENTIALITY PROCEDURES

Copies of the signed informed consents will be kept in a secure location. Participating sites will be expected to secure their patient private health information in a similar manner, in accordance with HIPAA guidelines. Each additional site must allow the coordinating center to perform on-site inspections of study data.

19.2 SUBJECT COSTS

There will be no additional costs to the patients. Any costs resulting from evaluating abnormal histology results will be considered standard medical practice for assessment of a suspicious breast biopsy result. As this is considered standard medical practice, the participant or their health care provider will be expected to pay these costs. It is also important to point out that costs of studies to investigate or treat any abnormalities found on physical exam or through the blood tests are not covered by the study.

19.3 PAYMENTS TO SUBJECTS

Participants will not be paid for participation in this study.

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47. Chloroquine package insert.

48. Paclitaxel package insert.

49. Docetaxel package insert.

50. Abraxane package insert.

51. Ixabepilone package insert.

21. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classifications

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

This table is an excerpt from the Oxford Textbook of Medicine, 2nd ed. Oxford; New York: Oxford University Press, 1987, p. 2228.

Appendix C: Version 4.0 (dated June-14-2010)

CTCAE Files

NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files and related documents are published here. The most current release files appear in this directory:

Files: Booklet	Content
CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf	Most recent release of core terminology: PDF document, traditional small booklet format.

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix D: WOCBP & Determination of Menopausal Status

WOCBP

Women of childbearing potential and men must agree to use adequate contraception (one of the following listed below) prior to study entry, for the duration of study participation and up to 90 days following completion of therapy. Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms for the duration of the study and for 90 days following completion of therapy.

- Total abstinence from sexual intercourse (minimum one complete menstrual cycle).
- Vasectomized male subjects or vasectomized partner of female subjects.
- Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration.
- Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream).
- Intrauterine device (IUD).

The following criteria will be used in the CAT trial to define postmenopausal:

- Age 56 or older with no spontaneous menses for at least 12 months prior to study entry; **Or**
- Age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) and with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard;

Or

- Documented bilateral oophorectomy.

Women failing to meet one of these criteria will be classified as pre-menopausal.

Appendix E: Chloroquine Drug Interactions

HALOFANTRINE	HALOFANTRINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
CIMETIDINE	CHLOROQUINE and CIMETIDINE may result in chloroquine toxicity (agitation, seizures, cardiac arrest).
GEMIFLOXACIN	GEMIFLOXACIN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
ISOFLURANE	ISOFLURANE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
HALOPERIDOL, RISPERIDONE, ZOTEPINE, SERTINDOLE, QUETIAPINE, AMISULPRIDE SULTOPRIDE	CHLOROQUINE and ANTIPSYCHOTICS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
DOLASETRON	CHLOROQUINE and DOLASETRON may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
FLUOXETINE	CHLOROQUINE and FLUOXETINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
TELITHROMYCIN	TELITHROMYCIN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
CHLORAL HYDRATE	CHLORAL HYDRATE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
VASOPRESSIN TANNATE	CHLOROQUINE and VASOPRESSIN may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
ZOLMITRIPTAN	ZOLMITRIPTAN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
RABIES VACCINE	RABIES VACCINE and CHLOROQUINE may result in decreased antibody response.
CLASS I ANTIARRHYTHMIC AGENTS FLECAINIDE, PROPAFENONE, APRINDINE.	CHLOROQUINE and CLASS I ANTIARRHYTHMIC AGENTS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
FLUCONAZOLE	CHLOROQUINE and FLUCONAZOLE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
COTRIMOXAZOLE	COTRIMOXAZOLE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
LIDOFLAZINE	LIDOFLAZINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
ARSENIC TRIOXIDE	ARSENIC TRIOXIDE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
CLASS IA ANTIARRHYTHMIC AGENTS QUINIDINE,DISOPYRAMIDE,PROCAINAMIDE, PIRMENOL,PRAJMALINE, AJMALINE HYDROQUINIDINE	CHLOROQUINE and CLASS IA ANTIARRHYTHMIC AGENTS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
MEFLOQUINE	MEFLOQUINE and CHLOROQUINE may result in an increased risk of convulsions, electrocardiogram abnormalities, cardiac arrest.
HALOTHANE	HALOTHANE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
ISRADIPINE	ISRADIPINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
TRICYCLIC ANTIDEPRESANTS NORTRIPTYLINE, DESIPRAMINE, IMIPRAMINE, AMITRIPTYLINE, DOXEPIN, AMOXAPINE TRIMIPRAMINE, PROTRIPTYLINE, DIBENZEPIN	CHLOROQUINE and TRICYCLIC ANTIDEPRESSANTS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
CLASS III ANTIARRHYTHMIC AGENTS BRETYLIUM,AMIODARONE, SOTALOL, ACECAINIDE, DOFETILIDE, IBUTILIDE,, SEMATILIDE, AZIMILIDE, TEDISAMIL	CHLOROQUINE and CLASS III ANTIARRHYTHMIC AGENTS may result in cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest).
SPIRAMYCIN	SPIRAMYCIN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
CLARITHROMYCIN	CHLOROQUINE and CLARITHROMYCIN may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
DROPERIDOL	DROPERIDOL and ANTIMALARIALS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

ASTEMIZOLE	ASTEMIZOLE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
ENFLURANE	ENFLURANE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
PROBUCOL	CHLOROQUINE and PROBUCOL may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
ERYTHROMYCIN	ERYTHROMYCIN and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
OCTREOTIDE ACETATE	OCTREOTIDE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
PHENOTHIAZINES: PROCHLORPERAZINE, CHLORPROMAZINE, TRIFLUOPERAZINE	CHLOROQUINE and PHENOTHIAZINES may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
FOSCARNET	FOSCARNET and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
PENTAMIDINE	PENTAMIDINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
CISAPRIDE MONOHYDRATE	CHLOROQUINE and CISAPRIDE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
BEPRIDIL HYDROCHLORIDE	BEPRIDIL and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
ZIPRASIDONE HYDROCHLORIDE	ZIPRASIDONE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
LEVOMETHADYL	LEVOMETHADYL and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
THIORIDAZINE	CHLOROQUINE and THIORIDAZINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
PIMOZIDE	CHLOROQUINE and PIMOZIDE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
MESORIDAZINE	CHLOROQUINE and MESORIDAZINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
AUROTHIOGLUCOSE	AUROTHIOGLUCOSE and CHLOROQUINE may result in an increased risk of blood dyscrasias.
TERFENADINE	TERFENADINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
BEPRIDIL HYDROCHLORIDE	BEPRIDIL and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
ZIPRASIDONE HYDROCHLORIDE	ZIPRASIDONE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
LEVOMETHADYL	LEVOMETHADYL and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
THIORIDAZINE	CHLOROQUINE and THIORIDAZINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
PIMOZIDE	CHLOROQUINE and PIMOZIDE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
MESORIDAZINE	CHLOROQUINE and MESORIDAZINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
AUROTHIOGLUCOSE	AUROTHIOGLUCOSE and CHLOROQUINE may result in an increased risk of blood dyscrasias.
TERFENADINE	TERFENADINE and CHLOROQUINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

Appendix F: List of Abbreviations

AE	adverse event
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CMF	cyclophosphamide, methotrexate, and fluorouracil
CMP	comprehensive metabolic profile
CR	complete response
CRF	Case Report Form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Center for Therapy Evaluation Programs
CYP450	cytochrome P450
DFS	disease-free survival
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ER	estrogen receptor
FDA	Food and Drug Administration
FEC	fluorouracil, epirubicin, and cyclophosphamide
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
HCl	hydrochloride
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act

HRT	hormone replacement therapy
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
LD	longest diameter
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MRI	magnetic resonance imaging
MUGA	multigated (radionuclide) angiogram
N/A	not applicable
NCI	National Cancer Institute
N/D	not done
NYHA	New York Heart Association
ORR	overall response rate
pCR	pathologic complete response
PD	progressive disease
PET	positron emission tomography
PHI	protected health information
PR	partial response
Pr	progesterone receptor
PVC	polyvinyl chloride
QA	quality assurance
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
TTP	time to tumor progression
ULN	upper limit of normal
WOCBP	woman of childbearing potential