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Modulation of autophagy with hydroxychloroquine in patients with advanced/recurrent non-small cell lung cancer – a Phase II study

[redacted]

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Drug(s) Under Investigation: hydroxychloroquine, carboplatin, paclitaxel and bevacizumab

CONFIDENTIAL

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute neutrophil count
CBC	Complete blood count
CINJOG	Cancer Institute of New Jersey Oncology Group
CT	computer tomography
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IRB	Institutional Review Board
kg	kilograms
mL	milliliters
mcg/μg	Micrograms
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PHI	Protected health information
PI	Principal Investigator
PR	Partial response
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious adverse event
SD	Stable disease
sCr	Serum creatinine
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
ULN	Upper limit of normal

1. Purpose/Specific Objectives

1.1 Primary Endpoint

1.1.1 The primary objective of this study is to assess the antitumor activity, as measured by tumor response rate, of paclitaxel, carboplatin, Bevacizumab (for eligible patients) and hydroxychloroquine in patients with advanced or recurrent NSCLC cancer.

1.2 Secondary Endpoint(s)

1.2.1 To measure time to progression, percent one-year survival and overall survival
1.2.2 To assess toxicity of this regimen
1.2.3 To correlate clinical response with k-ras mutations

2. Background and Significance

Lung Cancer

Lung cancer is the number one cause of cancer-related mortality in the United States, with an estimated 160,390 deaths in 2007.[1] Over 85% of these patients will have non-small cell lung cancer (NSCLC), and the majority of these patients have advanced disease at the time of diagnosis. Patients with advanced disease who have an adequate performance status (PS) clearly benefit from systemic chemotherapy, and many clinical trials were conducted to determine the most effective regimen. In the late 1990's, the Eastern Cooperative Oncology Group (ECOG) conducted a randomized phase III trial (E1594) to compare outcomes associated with several platinum-based regimens: cisplatin + vinorelbine, cisplatin + paclitaxel, cisplatin + docetaxel, and carboplatin + paclitaxel.[2] There were no significant differences in overall survival (OS) between the 4 arms, with a median survival of 7.9 months and a 1-year survival rate of 33%, although patients receiving carboplatin + paclitaxel experienced the least toxicities. Similar findings were observed in a trial conducted by the Southwest Oncology Group (SWOG), in which carboplatin + paclitaxel was compared to cisplatin + vinorelbine.[3] Again median survival was 8 months with a 1-year survival rate of 36-38%. As many patients with NSCLC are elderly or have co-morbidities that preclude the use of cisplatin, a large meta-analysis comparing platinum-based doublet regimens to non-platinum based, third generation regimens revealed that survival outcomes between these regimens were also not significantly different. [4] It was proposed that the addition of a third cytotoxic agent could improve survival, a question that was addressed in many clinical trials. However the majority of these studies demonstrated increased toxicity without an additional statistically significant benefit in survival.[5-7] Therefore, the current standard therapy includes two cytotoxic agents, one of which is usually a platinator if tolerable. However, the poor outcomes still associated with advanced NSCLC clearly demanded the need for continued improvements in treatment.

Angiogenesis and vascular endothelial growth factor

Scientific evidence supports the hypothesis that the growth of solid tumors is dependent on neo-angiogenesis which led to the development of a novel approach in treatment.[8-10] Delivery of oxygen and nutrients by the new vessels is a rate-limiting step for tumor cell proliferation and growth. Thus, tumor-associated vasculature is a target for anti-tumor therapy. This concept of

neo-angiogenesis led to the identification of factors responsible for stimulating new blood vessel formation. Vascular endothelial growth factor (VEGF), an endothelial cell-specific mitogen, was identified as a major regulator of angiogenesis implicated in turning on the angiogenic switch necessary for progressive tumor growth.[11] VEGF is a highly conserved, homodimeric glycoprotein whose dominant isoform has a molecular mass of about 45 KD, and has a well-defined role in normal and pathologic angiogenesis.[12, 13] VEGF stimulates proliferation of vascular endothelial cells, with a mean effective concentration (concentration resulting in 50% of maximal achieved proliferation) of 10-50 pM. VEGF gene expression is substantially increased in a majority of human tumors, including lung tumors, when compared with the surrounding tumor-free tissues.[14] A correlation was noted between the degree of tumor vascularization and the level of VEGF mRNA expression.[15-19] In virtually all specimens examined, VEGF mRNA is expressed in tumor cells but not endothelial cells. In contrast, mRNAs for two VEGF receptors, VEGFR1 and VEGFR2, are upregulated in endothelial cells associated with the tumor. These findings are consistent with the hypothesis that VEGF is primarily a paracrine mediator responsible for stimulating neo-angiogenesis and tumor propogation (18)

Targeting angiogenesis results in improved outcomes in select patients with NSCLC

Based on these data, investigators postulated that anticancer therapy could be significantly improved by not only targeting the tumor cells directly, but also by targeting neo-angiogenesis.[20] Bevacizumab is a recombinant humanized monoclonal antibody that binds to VEGF-A, preventing: binding to VEGFR-1 and -2 and downstream activation of endothelial growth and migration. In early clinical trials, bevacizumab demonstrated minimal toxicity in combination with chemotherapy.[21, 22] A randomized phase II trial demonstrated a significant improvement in time to progression (TTP) in patients receiving carboplatin, paclitaxel and bevacizumab (15 mg/kg) compared to chemotherapy alone (7.4 mo vs. 4.2 mo, p=0.02).[23] However, life-threatening and fatal hemorrhage was observed in 9% of patients, and further analysis linked this toxicity to tumors of squamous cell sub-histology. Thus patients with squamous cell tumors, as well as those with a prior history of hemoptysis or brain metastases have been excluded from all further clinical trials using bevacizumab. The prospectively randomized study of bevacizumab in NSCLC was conducted by ECOG (E4599) in which patients with advanced non-squamous NSCLC received carboplatin + paclitaxel with or without bevacizumab.[24] This trial met its primary endpoint of an improvement in median OS (12.3 vs. 10.3 mo, HR 0.80, p=.013) in patients receiving chemotherapy plus bevacizumab as compared to patients receiving chemotherapy alone. There was also an improvement in response rate (35% vs 15%, p<.001) and PFS (6.2 vs 4.5 mo, p<.0010). These significant improvements were accompanied by an increase in toxicity and treatment related death (3% vs 1%, p<.001). Based on these results the combination of carboplatin, paclitaxel and bevacizumab was approved by the FDA in Oct 2006 for the first line treatment in patients with advanced non-squamous NSCLC and has become a standard of care in the USA for these patients with a good PS.

Since wound healing requires neovascularization, in clinical practice, those patients who underwent a recent procedure (such as port placement, recent invasive procedure where there is a need for wound healing), should receive Bevacizumab only after a 4 to 6 week delay for wound healing.

Bevacizumab Ineligible patients:

For these reasons, recent studies now distinguish patients with lung cancer into at least two cohorts, those who are eligible for Bevacizumab and those who are not[25]. Typically, patients with NSCLC without contraindications (hemoptysis, squamous histology, brain metastasis) are considered as Bevacizumab eligible while the others are considered Bevacizumab ineligible. Bevicizumab eligible patients will be defined as Cohort 1 in this study. These patients will receive paclitaxel, carboplatin, bevacizumab and hydroxychloroquine.

Standard treatment for patients who are Bevacizumab ineligible is one of the standard chemotherapies as per the ECOG 1594. [2] Carboplatin and Paclitaxel is one of the standard regimens and thus will be used as the back bone of the chemotherapy for Bevacizumab ineligible patients as well. These patients will be defined as Cohort 2. These patients will receive paclitaxel, carboplatin, and hydroxychloroquine.

Autophagy: a cell survival mechanism

While targeting angiogenesis has resulted in improved outcomes in NSCLC, the lack of durable responses points towards resistance mechanisms. One such possible resistance mechanism is through the activation of cell survival pathways such as autophagy. Autophagy is a normal, well-regulated cellular response that is activated during times of nutrient deprivation. Autophagy is effectively the cells recycling program whereby autophagosomes containing sequestered cytoplasmic material fuse with lysosomes, resulting in digestion and reutilization of these cellular contents.[26] This process temporarily conserves cellular energy, limits the accumulation of damaged proteins and organelles during cellular stress, and thereby promotes cellular survival. In tumor cells with defects in apoptosis (also known as programmed cell death) autophagy allows for sustained viability and the ability to tolerate metabolic stresses.[27-31] This process may allow cells to survive in a "spore-like" resistant state temporarily. This may eventually result in cell death, but the restoration of nutrients allows these cells to regenerate.[27, 29, 32] In those tumor cells with defects in apoptosis, and which rely on autophagy to survive, inhibitors of autophagy can induce necrotic cell death.[30] Alternatively, in tumor cells with intact apoptotic pathways, inhibition of autophagy can increase apoptotic cell death.[33] Thus blocking autophagy has the potential to increase tumor cell death by several different pathways. Studies by White laboratory [33a] in engineered mouse lung cancer models demonstrated that k-ras mutant mice depend on autophagy, and autophagy inhibition inhibits tumor development and progression.

Autophagy: potential mechanism of resistance to anti-angiogenic therapy

Recent studies have shown that K5 and endostatin, potent angiogenesis inhibitors, also induce autophagy in endothelial cells of different tumor types.[34] If autophagy is induced by treatment with angiogenesis inhibitors, the autophagic pathway may promote tumor escape from the effects of antiangiogenic agents. A common feature of K5 and endostatin is upregulation of Beclin1, the mammalian homologue of the yeast *Atg6* autophagy gene involved in regulation of early autophagosome formation, leading to alterations in the Beclin1-Bcl-2 complex. Interfering with this autophagic response by knocking down Beclin1 levels, thus abrogating autophagy, dramatically increased apoptotic cell death of endothelial cells. Clinically antiangiogenic agents

such as bevacizumab can induce metabolic stress through nutrient deprivation, a process that may be enhanced using drugs that target autophagy.

Hydroxychloroquine is an agent that has been in use in the clinic for some time for the treatment of malaria, rheumatoid arthritis, and systemic lupus erythematosus. This agent works through inhibition of lysosomal acidification and blocks autophagy. Indeed the addition of chloroquine to either antiangiogenic agents or cytotoxic agents significantly increases antitumor activity.[30, 32, 35] In this trial we hypothesize that the addition of hydroxychloroquine to the standard regimen of paclitaxel, carboplatin with or without bevacizumab will significantly increase antitumor activity.

The initial phase I study of this combination defined the dose in the first cohort of patients (n=8) and demonstrated toxicity similar to the chemotherapy combination without the addition of the hydroxychloroquine. A review of the response data showed that 6 of the 8 patients achieved a partial response by RECIST criteria. Subsequent interim analysis of this and the prior study shows a composite 52% PR, and 25% Stable disease rate. The progression free and overall survival data are as yet ongoing but easily comparable to or better than historical data for stage IV disease. Given the initial promising results in objective response, further phase II testing of this combination seem warranted.

Hydroxychloroquine:
Hydroxychloroquine is a 4-aminoquinoline that has been in use for more than 30 years for the treatment of malaria, rheumatoid arthritis, and systemic lupus erythematosus. A dose of 200 mg po bid is well tolerated for chronic use and doses up to 1200 mg/day have been widely used safely. Pharmacokinetic data from the Cancer Institute of New Jersey phase I studies, similar to studies in Rheumatoid arthritis, have shown that with daily dosing, the hydroxychloroquine remains membrane bound, but free levels are seen in 1200 mg/day. A total equivalent daily dose was well tolerated by patients with rheumatoid arthritis, without any reported adverse events or need to discontinue drug secondary to toxicity during the first year of treatment.[41] In this study the majority of toxicity was attributable to gastrointestinal issues, anemia and rash. An extremely rare toxicity of hydroxychloroquine is ocular toxicity that can result in retinopathy with visual field deficits. This toxicity is related to the daily and cumulative dose of drug, as well as the duration of therapy, and is even more rare before 2 years of therapy.[42] Given the rarity of this toxicity, the relatively short expected duration of therapy, and the lack of any adverse ocular findings in our (and other's) oncology trials, we will forgo ocular monitoring, but remain cognizant of this rare toxicity.

Hydroxychloroquine has dramatically entered cancer clinical trials and NCI lists 29 clinical trials involving hydroxychloroquine. Addition of hydroxychloroquine to adjuvant chemotherapy and radiotherapy for patients with glioblastoma multiforme in a small pilot study resulted in prolongation of median survival, which though not statistically significant due to the small number of patients enrolled, is worth further exploration in larger trials (49) At present, hydroxychloroquine is being tested in combination with radiation therapy and temozolomide for the treatment of patients with newly diagnosed glioblastoma multiforme in a large multi-center NCI-sponsored clinical trial (NCT00486603), and in combination with bortezomib in patients with relapsed or refractory multiple myeloma in another NCI-sponsored study (NCT00568880). At the [redacted] we have a portfolio of studies testing autophagy inhibition

with hydroxychloroquine and we closed a dose finding study in NSCLC which provides the dosing for this Phase II study.

2.1 Study Rationale

This is an open-label Phase II study of paclitaxel, carboplatin, and bevacizumab (in Bevacizumab eligible patients) plus hydroxychloroquine in the treatment of patients with advanced NSCLC. Our hypothesis is that inhibition of autophagy using hydroxychloroquine will improve the activity of standard chemotherapy +/- bevacizumab in this patient population. Our Phase I study (030801) showed tolerability at standard doses of all agents and also showed considerable activity in response (see statistical design). Hydroxychloroquine is a moderate inhibitor of CYP 2D6 and a major substrate of that enzyme, and there is both hepatic and renal clearance of drug.[43] Paclitaxel is major substrate of CYP2C8 and 3A4, a minor inducer of CYP3A4; carboplatin is subject to renal clearance; bevacizumab is subject to proteolytic catabolism throughout the body.

We will also perform exploratory correlative analyses of LC3 protein expression on peripheral blood mononuclear cells, and Beclin-1 and p62 expression in pretreatment tumor tissue, when available. LC3 is a marker of autophagosome formation. Beclin-1 is an essential regulator of autophagy and levels of this protein may correlate with and/or indicate the capacity for autophagy, and p62 accumulation is associated with autophagy. These analyses will be considered exploratory as there are no established markers of autophagy.

3. Participating Institutions

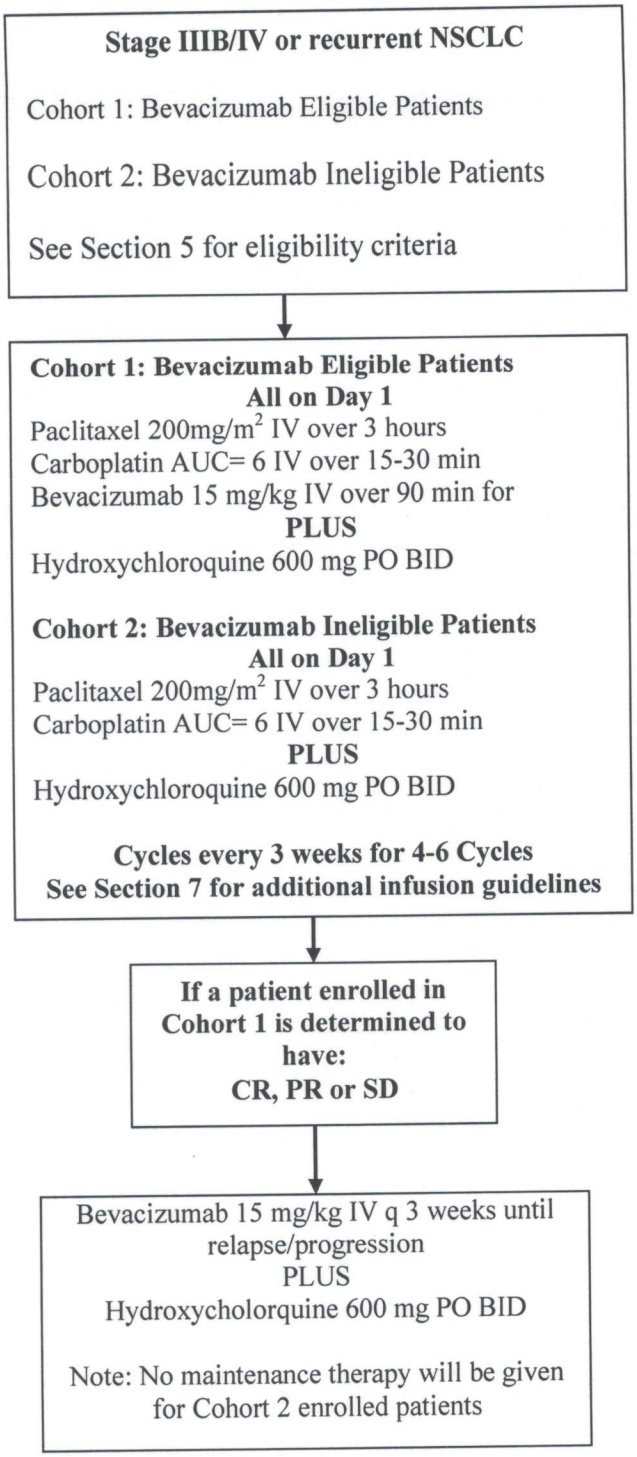
[redacted]

4. Experimental Design and Methods

This is an open-label Phase II study of the combination of paclitaxel at 200 mg/m^2 intravenously over 3 hours on Day 1; followed by carboplatin AUC = 6 intravenously over 15-30 minutes on Day 1 followed by Bevacizumab (for Cohort 1) at 15 mg/kg intravenously (initial infusion over 90 minutes) on Day 1; and hydroxychloroquine orally (600 mg BID) on Days 1-21. Chemotherapy will be repeated every 21 days for a total of 6 cycles if tolerated. The total number of cycles will be determined by the treating physicians in agreement with the Principal Investigator. Patients in Cohort 1 will then continue to receive bevacizumab every 21 days and hydroxychloroquine daily up to 1 year until evidence of disease progression or unacceptable toxicity, while Cohort 2 will receive hydroxychloroquine alone. The continuation of the hydroxychloroquine (with or without bevacizumab as per cohort) is based on several recent studies suggesting improved disease free and overall survival with maintenance therapy [24, 35, 36], and continuation of hydroxychloroquine could spare the patients the accumulating toxicity of continued chemotherapy.

After baseline evaluation, tumor response will be evaluated every 2 cycles (6 weeks) of therapy. Responses will be assessed using RECIST criteria. Patient survival will be followed every 2-3 months after completion of initial chemotherapy until progression of disease, and followed for overall survival.

Schema:


Stage IIIB/IV or recurrent NSCLC
Cohort 1: Bevacizumab Eligible Patients
Cohort 2: Bevacizumab Ineligible Patients
See Section 5 for eligibility criteria
Cohort 1: Bevacizumab Eligible Patients
All on Day 1
Paclitaxel 200mg/m2 IV over 3 hours
Carboplatin AUC= 6 IV over 15-30 min
Bevacizumab 15 mg/kg IV over 90 min for
PLUS
Hydroxychloroquine 600 mg PO BID
Cohort 2: Bevacizumab Ineligible Patients
All on Day 1
Paclitaxel 200mg/m2 IV over 3 hours
Carboplatin AUC= 6 IV over 15-30 min
PLUS
Hydroxychloroquine 600 mg PO BID
Cycles every 3 weeks for 4-6 Cycles
See Section 7 for additional infusion guidelines
If a patient enrolled in Cohort 1 is determined to have:
CR, PR or SD
Bevacizumab 15 mg/kg IV q 3 weeks until relapse/progression
PLUS
Hydroxycholorquine 600 mg PO BID
Note: No maintenance therapy will be given for Cohort 2 enrolled patients

4.1 Duration of Study

The anticipated time a patient will be on study will be up to approximately 12-18 months (6 cycles of chemotherapy/+/-Bevacizumab/hydroxychloroquine followed by up to 1 year of chemotherapy/+/-Bevacizumab/hydroxychloroquine for Cohort 1 or 2 respectively. A longer time on follow-up would be a reflection of a very positive outcome of the study.

Approximately 40 patients will be enrolled on this study. This study is expected to accrue 12-15 patients a year (based on prior accrual history, see protocol 030302) for 3 years.

5. Patient Selection Criteria

5.1 Inclusion Criteria

A patient is eligible for enrollment if all of the following inclusion criteria are met

5.1.1. Signed a protocol-specific informed consent.
5.1.2. 18 years of age or older.
5.1.3. ECOG Performance Status 0 or 1. (see Appendix A)
5.1.4. Tumor assayed for k-ras and other tumor genomic mutations

Cancer criteria:

5.1.5. Histologically or cytologically confirmed non-small cell lung cancer. Mixed tumors will be categorized by the predominant cell type unless small cell elements are present, in which case the patient is ineligible. Cytologic or histologic elements can be established on metastatic tumor aspirate or biopsy. Sputum cytology alone is not sufficient.
5.1.6. Advanced stage NSCLC (stage IVa ((malignant pleural effusion (is now staged as stage IVa by the most recent staging system), or stage IV, or recurrent disease)).
5.1.7. Measurable disease according to RECIST criteria.
5.1.8. Patient with CNS metastasis are required to have stable disease documented by being off treatment (surgery, or Whole Brain radiation therapy) for at least 2 weeks, and four (4) weeks is preferred. No delay in onset of therapy is required for those patients who undergo stereotactic RT to the brain lesion(s). A contrast enhanced brain CT or brain MRI is required within 35 days of enrollment. Patients with brain metastases who qualify for protocol therapy will be included in Cohort 2 (ineligible for treatment with Bevacizumab).
5.1.9. No prior cytotoxic chemotherapy or targeted therapy in the advanced or metastatic setting. Post-operative adjuvant therapy for previously resected NSCLC is allowed as long as the last dose was given greater than 1 year before study entry, and there is current evidence of disease progression.
5.1.10. Prior radiation to sites *other than the brain* is allowed, if completed at least 2 weeks before treatment and provided that all radiation-related toxicities have resolved to $\leq$ Grade 1. Stereotactic irradiation to any site excludes the need for a waiting period.
5.1.11. No active malignancy other than NSCLC. Patients with a history of basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, or ductal or lobular carcinoma in situ of the breast within the past 3 years must have been treated

with curative intent. Patients with a history of prior malignancy are eligible provided they were treated with curative intent and have been free of disease for > 3 years.

Laboratory requirements

5.1.12. Adequate organ function, as evidenced by ALL the following:

- absolute neutrophil count (ANC) ≥ 1500/mm³
- platelet count ≥ 100,000/mm³
- hemoglobin ≥ 9 gm/dL
- total bilirubin ≤ 1.5 x ULN; if patient has Gilbert's disease, then patient must have isolated hyperbilirubinemia (e.g. no other liver function test abnormality), with maximum bilirubin ≤ 2 X institutional ULN.
- AST and ALT ≤ 2.5 x ULN in the absence of liver metastases;
  AST and ALT ≤ 5 x ULN in the presence of liver metastases
- alkaline phosphatase ≤ 2.5 x ULN
- creatinine ≤ 1.5 X institutional ULN or calculated creatinine clearance ≥ 60 ml/min as estimated using the Cockroft-Gault formula.

Comorbidities

For Cohort 1: (Bevacizumab eligible)

5.1.13. No history of gross hemoptysis (defined as bright red blood of a half-teaspoon or more) within 3 months prior to enrollment.

5.1.14. None of the following conditions within 6 months prior to enrollment: myocardial infarction, stroke or symptomatic peripheral vascular disease.

5.1.15. For patients who have had a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to enrollment, or anticipate the need for such while on active treatment, may participate and receive Bevacizumab at the start of the second or third cycle as they would under standard care. Placement of vascular access device is not considered major surgery, but the incision must have healed before initiation of treatment.

5.1.16. No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to enrollment.

5.1.17. No serious non-healing wound, ulcer or bone fracture.

5.1.18. Patients must have a systolic blood pressure ≤ 150 mm Hg and diastolic blood pressure ≤ 100 mm Hg (the use of antihypertensive medications to achieve these goals is allowed).

5.1.19. Patients must not have unstable angina or NYHA classification of congestive heart failure of Grade ≥ 2 (see Appendix B).

5.1.20. No history of significant vascular disease (eg aortic aneurysm).

5.1.21. No current or recent (within 28 days of enrollment) full dose anticoagulants or thrombolytic agents.

5.1.22. Adequate organ function

- INR ≤ 1.5 and aPTT WNL.
- Urine Protein Creatinine (UPC) ratio < 1.0 or 24 hour urine protein ratio < 1000 mg

UPC ratio of spot urine is an estimation of the 24 urine protein excretion. A UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. To obtain a UPC ratio:

- *Obtain at least 4 mL of a random urine sample*
- *Determine protein and creatinine concentration*
- *Calculate the UPC using one of the following formulae*

[urine protein]/[urine creatinine] – if both values are reported in mg/dL

[(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

For Cohort 2 (Bevacizumab ineligible):

5.1.23. None of the following conditions within 6 months prior to enrollment: myocardial infarction, stroke or symptomatic peripheral vascular disease.

5.1.24. Patients must not have unstable angina or NYHA classification of congestive heart failure of Grade ≥ 2 (see Appendix B).

5.1.25. Patients must not have hemoptysis, squamous histology, brain metastasis

For ALL (Cohort 1 and Cohort 2):

5.1.26. Patients must not have psoriasis or porphyria.

5.1.27. No known hypersensitivity to 4-aminoquinoline compound.

5.1.28. Patients must not have known or suspected G-6P deficiency.

5.1.29. No know bleeding diathesis or coagulopathy.

5.1.30. No known GI pathology that would interfere with drug bioavailability.

5.1.31. No peripheral or sensory neuropathy > Grade 1 at study entry.

5.1.32. No known prior hypersensitivity to carboplatin, paclitaxel, bevacizumab or hydroxychloroquine or any of their components.

5.1.33. No ongoing or active infection at study entry.

5.1.34. Patients must not be receiving treatment for rheumatoid arthritis or systemic lupus erythematosus.

5.1.35. Patients must not have HIV or be taking HAART therapy.

5.1.36. Patients must not have a history of any condition (social or medical) that, in the opinion of the Investigator, might interfere with the patient's compliance with the protocol or pose additional or unacceptable risk to the patient.

5.1.37. Women must NOT be pregnant or breastfeeding.

5.1.38. Women must :

- Have a negative serum or urine pregnancy test within 7 days prior to study entry if she is a woman of child-bearing potential, OR
- Be at least one year post-menopausal, OR
- Be surgically sterile

5.1.39. Patients of childbearing or child fathering potential must be willing to use an acceptable method of birth control prior to study entry and for the duration of the

study. Acceptable methods of contraception include hormonal, barrier methods, intrauterine device, tubal ligation/vasectomy or abstinence.

5.1.40. Must not be taking hydroxychloroquine for treatment or prophylaxis of malaria.

5.2 Inclusion of Women and Minorities

The National Institute of Health (NIH) and NCI have stressed the importance of gender and minority inclusion in clinical services and research. Female patients accounted for 58% of cancer patients seen within The Cancer Institute of New Jersey's clinical programs within the last year. African-Americans comprised 7%, Hispanics 8%, and Asians 3% of female patients, respectively. For all patients entering clinical trials, the percentages were 52% women, 6% African-American, 5% Hispanic, and 3% Asian.

No person shall, on the grounds of age, race, color, or national origin, be excluded from participation in, or be denied the benefits of, enrollment in this protocol.

5.3 Participation of Children

Patients under the age of 18 will be excluded from study participation. Lung cancer is not seen in the pediatric population

5.4 Sources or Methods of Recruitment

Participants for this study will be recruited from the patient population evaluated and treated at the [redacted]

5.5 Study Enrollment Procedures

A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at [redacted]

[redacted] patient does not receive any protocol therapy, baseline data will be collected and submitted on the pre-study and follow-up electronic case report forms (eCRF). The reason for not starting protocol therapy will be documented in the "follow-up eCRF". Case report form completion instructions and training will be provided to each participating institution prior to study activation at the participating institution.

6. Study Parameters

The following tests and evaluations will be performed according to the schedule below. Baseline (i.e., pre-study) evaluations must be performed no longer than 4 weeks (+/- 3 days) prior to therapy, unless otherwise indicated in one of the footnotes below the table

		Chemotherapy Phase (Cycles 1-6)[h]			Post-Chemotherapy Phase			
Evaluations	Screening	Every cycle	Every week	Every 2 cycles	Every cycle	Every 3 cycles	Other	End of Treatment
Signed Informed Consent	X							
Initial History & Physical	X							
Interim History & Physical		X			X			X
Concurrent medications	X	X			X			
Toxicity Assessment		X	X		X			X
ECOG Performance Status	X	X			X			X
Height, weight	X	X			X			
CBC, differential, platelets	X[a]	X[b]	X		X[b]			X
Serum Chemistries[c]	X[a]	X[b]			X[b]			X
INR,aPTT	X[a i]							
UPC[d]	X			X[b,d]		X[d]		X
Creatine phosphokinase (CPK)[e]	X						X[e]	
Pregnancy Test[f]	X							
Tumor Assessments[g]	X			X		X		
Brain CT/MRI	X							
Compliance Assessment					X			
Tumor tissue, if appropriate[j]	X							

a Within 1 week of enrollment.
b May be performed 72hr prior to Day 1. Screening lab results are acceptable for Cycle 1, Day 1 and do not need to be repeated.
c Includes: Electrolytes, Calcium, BUN, Creatinine, Total Protein, Glucose, Albumin, Total Bilirubin, Alk Phosphatase, AST/ALT
d For bevacizumab patients only - UPC to be obtained at baseline and at least every other cycle (Cycle 2, 4, 6, etc). If a UPC is not obtained on alternate cycles (Cycle 3,5,7, etc.), a urine dip must be obtained. If UPC ratio is > 1 a 24 hour urine for protein is to be collected
e Every 3 months while on trial regardless of phase of treatment
f. Women must: Have a negative serum or urine pregnancy test within 7 days prior to study entry if she is a woman of child-bearing potential [WOCBP], OR Be at least one year post-menopausal, OR Be surgically sterile.
g Tumor assessment (at a minimum CT Chest with liver and adrenal windows, with contrast if no contraindication) of all known lesions are to be evaluated according to RECIST. RECIST criteria will be completed on or before the day of treatment prior to drug delivery. Any PR or CR must be confirmed by repeat radiographic assessment performed at least 4 weeks (+/- 3 days) after the prior scan. This confirmatory scan will serve as a new baseline, and tumor assessment can be performed every 2 cycles starting from the time the confirmatory scan is obtained.
h Patients may receive up to 6 cycles as determined appropriate by the attending physician in agreement with the Principal Investigator.
i INR will be determined for bevacizumab patients only.
j. Access archived tumor tissue at time of diagnosis or repeat diagnostic biopsy at screening, where appropriate (e.g. when time from diagnosis to presentation may warrant)

7. Treatment Plan

7.1 General Considerations

Treatment will be administered on an outpatient basis. A cycle is defined as an interval of 21 days (a delay of 2 days due to holidays, weekends and bad weather will be permitted and will not be counted as a protocol violation). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Patients will receive treatment until it is no longer of benefit to them or until 1 year. Patients may discontinue therapy at any time for any reason.

7.2 Study Agents

Hydroxychloroquine

Hydroxychloroquine will be obtained commercially and is available in a 200 mg tablet that is equivalent to 155 mg hydroxychloroquine base and 250 mg chloroquine phosphate. Hydroxychloroquine may be taken with food or milk at any time of the day. Once hydroxycholoroquine is started, patients should take hydroxychloroquine around the same time every day.

For patients that are unable to swallow capsules or tablets, the tablet may be removed and be dissolved in 5 ml of water or mixed in a small amount of liquid or food. However, the drug may be bitter-tasting. The drug may be dissolved in 5 ml of water for NG administration.

Patients receiving antacids, sucralfate, cholestyramine, and/or bicarbonate should have the study drug dose administered at least 1 hour before or 2 hours after these medications.

Carboplatin

Carboplatin will be obtained commercially and is available as a premixed sterile aqueous solution of 10mg/ml ready for dilution and parenteral administration. Vials are available in 50, 150, 450 and 600 mg sizes, contain no preservative, and are for single use only. For further details, refer to the Paraplatin® Package Insert and institutional standards.

Paclitaxel

Paclitaxel will be obtained commercially and is available as a concentrated solution of 6 mg/ml in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol 50% in 5, 16.7 and 50 ml vials. For further details, refer to the Taxol® Package Insert and institutional standards.

Bevacizumab

Only patients in Cohort 1 will receive Bevacizumab. Bevacizumab will be obtained commercially and is available as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400 or 100 mg (25 mg/ml) glass vial contains bevacizumab with a vehicle consisting of sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are for single use only. Vials should be refrigerated at 2°C-8°C (36°F-46°F) and should remain refrigerated unti use. Vials should be protected from light, not frozen, and not shaken. For further details, refer to the Avastin® Package Insert and institutional standards.

7.3 Dose Calculation

Hydroxychloroquine

Hydroxychloroquine will be given as a flat dose of 600 mg orally BID (total daily dose of 1200 mg). **Missed Doses**

If patients vomit after taking hydroxychloroquine, patients should be instructed not to retake the dose. Patients should take the next dose at the scheduled time.

If a scheduled dose is missed, patients should be instructed to take the dose as soon as remembered. If it is near the time of their next dose they should be instructed to skip the dose and resume their usual dosing schedule. Patients should not double their dose to catch up missed doses.

Paclitaxel

Paclitaxel will be given at a dose of 200 mg/m^2. The dose will be based on the patient's actual weight at screening in the determination of body surface area. A variance of 5% of the calculated total dose will be allowed.

BSA (m^2) =

$$\sqrt{\frac{height(in)xweight(lbs)}{3131}} \quad \text{or} \quad \sqrt{\frac{height(cm)xweight(kg)}{3600}}$$

Carboplatin

The dose will be AUC = 6 Carboplatin dose will be based on the Calvert formula:

Carboplatin dose (mg) = AUC x (GFR* +25)

*GFR is estimated using the Cockroft-Gault formula for creatinine clearance and the patient's corrected body weight (lean):

$$\frac{\{(140 - \text{patient's age}) \times (\text{patient's corrected body weight in kilograms})\}^{\#}}{(72 \times \text{patient's serum creatinine})}$$

#For females, multiply the result by 0.85

Ideal body weight = (2.3 * {inches over 5 feet}) + 45 kg for females
(2.3 * {inches over 5 feet}) + 50 kg for males

Corrected or Lean Body Weight =
({Total Body Weight – Ideal Body Weight} * 0.4) + Ideal Body Weight

Bevacizumab

Only patients in Cohort 1 will receive Bevacizumab. Bevacizumab will be given at a dose of 15 mg/kg. Doses will be calculated based on the patient's actual weight in kilograms at screening. A variance of 5% of the calculated total dose will be allowed.

7.4 Treatment Administration

This study will be open to the CINJOG Network hospital(s) and investigator offices.. Patients will be enrolled in one of two cohorts as determined by their type of cancer. Cohort 1 patients will be Bevicizumab eligble patient and Cohort 2 will be Bevicizumab ineligible patients.

Cohort 1 (Bevicizumab eligible)

Patients will be given paclitaxel at 200 mg/m^2, bevacizumab 15 mg/kg, carboplatin AUC = 6 and hydroxychloroquine 600 mg orally BID (total daily dose of 1200 mg).

Once hydroxycholoroquine is started, patients should take hydroxychloroquine around the same time every day.

Paclitaxel will be given by IV over 3 hours on Day 1 (see Section 7.4.1 for premedication guidelines and Section 7.3 for dosing information).

Carboplatin will be given at AUC = 6 by IV over 15-30 minutes on Day 1 immediately following paclitaxel (see Section 7.3 for dosing information).

Bevacizumab will be given by IV as detailed below on Day 1 immediately following carboplatin (see Section 7.3 for dosing information; Section 7.4.2 for infusion information). For patients that have had a recent surgery, or invasive procedure, Bevacizumab can be started at Cycle 2 or Cycle 3.

If a patient enrolled in Cohort 1 is determined to have complete response (CR), partial response (PR) or stable disease (SD) they will be given bevacizumab 15 mg/kg IV every 3 weeks and hydroxychloroquine 600 mg orally BID until relapse or progression occurs.

Cohort 2 (Bevicizumab ineligible)

Patients will be given paclitaxel at 200 mg/m^2, carboplatin AUC = 6 and hydroxychloroquine 600 mg orally BID (total daily dose of 1200 mg).

Once hydroxycholoroquine is started, patients should take hydroxychloroquine around the same time every day.

Paclitaxel will be given by IV over 3 hours on Day 1 (see Section 7.4.1 for premedication guidelines and Section 7.3 for dosing information).

Carboplatin will be given at AUC = 6 by IV over 15-30 minutes on Day 1 immediately following paclitaxel (see Section 7.3 for dosing information).

7.4.3. Paclitaxel premedications

Prior to receiving paclitaxel, all patients will receive the following premedication:

- Dexamethasone 20 mg po 12 and 6 hours prior to paclitaxel infusion (patients may be treated with dexamethasone 20 mg iv < 1 hour prior to infusion with paclitaxel if the patient did not take the oral dexamethasone)
- Diphenydramine 50 mg iv (or equivalent) < 1 hour prior to paclitaxel infusion
- Ranitidine 50 mg iv < 1 hour prior to paclitaxel infusion (alternatively other H2-blockers may be used)

7.4.1. Bevacizumab infusion (Cohort 1 – Bevacizumab eligible patients Only)

Bevacizumab will be given on Day 1 of each 21-day cycle. The initial bevacizumab dose will be delivered over 90 (±10) minutes as a continuous infusion. If a patient experiences an infusion-associated adverse event, he or she may be premedicated for the next drug infusion. However the infusion time may not be decreased for the subsequent infusion. If a patient continues to experience infusion-associated adverse events with the 90-minute infusion, the patient's symptoms should be managed per institutional guidelines. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (±10) minutes. If a patient experiences infusion-associated adverse events with the 60-minute infusion, all subsequent doses will be given over 90 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. If a patient experiences infusion-associated adverse events with the 30-minute infusion, all subsequent doses will be given over 60 minutes.

Monitoring for and management of anaphylactic reactions will be performed according to institutional guidelines.

7.5 Dose Modifications

Dose Modifications General Guidelines Cycles 1-6

All toxicities should be graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

DOSE MODIFICATIONS FOR ALL DRUGS WILL BE MADE USING THE FOLLOWING GENERAL GUIDELINES:

- The guidelines below are recommendations. Any toxicities observed should be managed according to institutional guidelines and the clinical judgment of the treating physician.
- All dose reductions are permanent.
- Dose modifications of any one drug will not affect the dose of the other 3 drugs.
- There are no dose reductions for bevacizumab. If adverse events occur that necessitate holding bevacizumab, the dose will remain unchanged once treatment resumes.

- If a dose is delayed due to toxicity, labs/toxicity should be reevaluated at least weekly until recovery to treatment levels, or as indicated in the dose modification tables.
- Regardless of the reason for holding any study drug treatment, the maximum allowable length of treatment interruption is 3 weeks. If the delivery of any study drug due to toxicity is delayed for more than 3 weeks, that drug should be permanently discontinued.
- Dose delay of either carboplatin, bevacizumab or paclitaxel will result in delay of the other drug (to ensure all drugs are delivered on the same day).
- Day 1 of each cycle will be based on the day that carboplatin and/or paclitaxel are delivered.
- If either paclitaxel or carboplatin are discontinued due to toxicity, day one of the cycle will be the day the remaining chemotherapy drug is delivered. The maximum delay of both drugs while monitoring toxicity is 3 weeks.
- If both chemotherapy drugs are discontinued due to toxicities despite dose reductions, the patient will come off study, and all therapy, including bevacizumab and hydroxychloroquine, will be discontinued.
- No more than 2 dose reductions for each chemotherapy drug will be allowed, and no more than one dose reduction of hydoxychloroquine. Bevacizumab dose reductions will not be allowed. Further need for dose reduction will result in discontinuation of that drug.

Dose Levels (Cycles 1 to 6)

	Paclitaxel dose	Carboplatin dose	Hydroxychloroquine
Starting dose	200 mg/m^2	AUC = 6	600 mg PO bid
Dose Level -1	175 mg/m^2	AUC = 5	400 mg PO bid
Dose Level -2	150 mg/m^2	AUC = 4	400 mg PO bid

7.5.1 Hematologic Toxicity

Absolute neutrophil count (paclitaxel, carboplatin)

- ANC must be $\geq 1500/mm^3$ on Day 1 of each cycle.
- If ANC $< 1500/mm^3$ on Day 1, treatment should be delayed by 1 week. Maximum delay is $\leq$ 3 weeks. Treatment should be restarted without dose modification, unless criteria in the table below are met.
- Dose modifications should be based on the nadir ANC and/or occurrence of febrile neutropenia during the previous cycle. For guidelines regarding the use of growth factors, see Section 7.7

Event during previous cycle

	Paclitaxel	Carboplatin	Bevacizumab/ Hydroxy-chloroquine
Nadir ANC < 500/mm^3 or febrile neutropenia (ANC < 1000/mm^3 and fever ≥38.5°C)	First occurrence: decrease dose by 1 dose level	First occurrence: decrease dose by 1 dose level	No change
	Second occurrence: may use CSFs in accordance with ASCO guidelines	Second occurrence: may use CSFs in accordance with ASCO guidelines	
	Third occurrence: decrease dose by 1 dose level	Third occurrence: decrease dose by 1 dose level	

Thrombocytopenia (paclitaxel, carboplatin)
Platelet count must be ≥ 100,000/mm^3 on day 1 of each cycle. If platelet <100,000/mm^3, treatment should be delayed by 1 week. Dose modifications should be based on the nadir platelet count during the previous cycle.

Event during previous cycle

	Paclitaxel	Carboplatin	Bevacizumab /Hydroxy-chloroquine
Nadir platelet count < 50,000/mm^3	Decrease dose by 1 dose level	Decrease dose by 1 dose level	No change

Anemia
No dose reductions will be made for anemia. Patients should receive supportive care, including erythropoietin, at the treating physician's discretion and as per guidelines in Section 7.7.

7.5.2 Non-Hematologic Toxicity

Hypertension (Bevacizumab-Cohort 1 only)

- Dose modifications for hypertension are applicable to bevacizumab dosing. No dose modifications are required for paclitaxel and carboplatin for hypertension.
- See Section 7.6 regarding concomitant medications (metoprolol)

Event during previous cycle

Hypertension	Dose Modification of Bevacizumab
Grade 0 - 2	No change, control hypertension with medications as per general therapy guidelines.
Grade 3	Hold drug until blood pressure can be controlled to ≤ 150/100 with standard medication. Restart drug at same dose.
Grade 4	Bevacizumab must be permanently discontinued.

Hepatic (paclitaxel)

- Liver function test will be evaluated prior to treatment on Day 1 of each cycle. This value should be used in determining the dose

SGOT (AST)		Bilirubin	Paclitaxel dose to give (mg/m^2)
≤ 5 x ULN	AND	WNL	200
> 5 x ULN	OR	>ULN – 1.5 x ULN	150
		> 1.5 x ULN	0

Gastrointestinal toxicity (all drugs)

- Any bowel obstruction ≥ Grade 2 will result in holding bevacizumab until resolution of symptoms. Patient may be restarted on bevacizumab at the discretion of the investigator
- Any GI perforation will result in discontinuation of patient from the study.
- Nausea and/or vomiting should be controlled with adequate antiemetics. Nausea and vomiting must be ≤ Grade 1 on Day 1 of each cycle. If nausea and vomiting are > Grade 1 on Day 1, then treatment will be delayed for up to 3 weeks.
- If the patient has any grade stomatitis or mucositis on Day 1 of any cycle, treatment will be withheld until full recovery.

- Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible.

Event during previous cycle

	Paclitaxel	Carboplatin	Bevacizumab	Hydroxychloroquine
Nausea or Vomiting Grade 3-4 despite antiemetics	First occurrence : Hold treatment until resolved to ≤ Grade 1, resume at previous dose Second occurrence : Hold treatment until resolved to ≤Grade 1, resume at previous dose			First occurrence : Hold treatment until resolved to ≤ Grade 1, resume at 50% dose Discontinue drug
Stomatitis or mucositis Grade 3-4	Decrease 1 dose level	Decrease 1 dose level	No change	No change
Diarrhea Grade 3-4	No change	No change	No change	Hold until resolved to ≤ Grade 1 then resume at 50% dose. If ≥ Grade 3 toxicity recurs at reduced dose, hydroxychloroquine must be permanently discontinued

Neurologic toxicity: neurosensory (paclitaxel)

- Neurologic toxicity must be ≤ Grade 1 on Day 1.
- If neurologic toxicity > Grade 1 on Day 1, treatment should be delayed by 1 week. Maximum delay is ≤ 3 weeks. Treatment should be restarted after dose modifications per guidelines below
- Dose reductions should be based on the most severe grade of toxicity experienced during the previous cycle of treatment or on Day 1.

Event during previous cycle

	Paclitaxel	Carboplatin	Bevacizumab/ Hydroxy-chloroquine
Grade 2	Allow recovery to ≤ Grade 1. Decrease by 1 dose level.	No change	No change
Grade 3	Allow recovery to	No change	No change

Event during previous cycle

	Paclitaxel	Carboplatin	Bevacizumab/ Hydroxy-chloroquine
Grade 2	Allow recovery to ≤ Grade 1. Decrease by 1 dose level.	No change	No change
	≤ Grade 1. Decrease by 2 dose levels.		

Anaphylaxis/Hypersensitivity (paclitaxel, carboplatin, bevacizumab)

Caution: patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

Event	Paclitaxel or Carboplatin or Bevacizumab Infusion
Mild (e.g., mild flushing, rash, pruritis, drug fever, ie. Grade 1)	No treatment needed. Supervise at bedside and complete infusion.
Moderate (e.g., moderate flushing, rash, mild dyspnea, allergy related edema, ie. Grade 2)	Stop drug infusion. Administer diphenhydramine 25-50 mg and dexamethasone 10 mg IV. After recovery, resume infusion per institutional guidelines. If no further symptoms occur, complete the infusion at the full dose rate. Report as an adverse event. Consider additional premedication with all subsequent doses of drug. If symptoms recur, permanently stop drug.
Severe (e.g., hypotension requiring pressors, angioedema, symptomatic bronchospasm: ie. Grade 3-4)	Stop drug infusion. Administer diphenhydramine 25-50 mg and dexamethasone 10 mg IV. Add epinephrine or bronchodilators as needed. Report as an adverse event. Permanently stop drug.

Hemorrhage

Event	Bevacizumab (Cohort 1 only)
Grade 1 pulmonary	Hold drug and evaluate for source. If resolved within 1 week, and no source, resume full dose. If recurrent, discontinue drug permanently.
Grade ≥ 2 pulmonary or CNS Grade 3 all other sites	Patients receiving full-dose anticoagulation must discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and hemoglobin is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence • Patients who experience recurrence of Grade 3 hemorrhage must discontinue study therapy.
Grade 4	Discontinue bevacizumab permanently.

Arterial Thrombosis (Bevacizumab – Cohort 1 only)

- Cardiac ischemia/ infraction
- CNS ischemia (TIA, CVA)
- Any peripheral or visceral arterial ischemia/thrombosis

Event	Bevacizumab
Grade 2 (if new or worsened since bevacizumab therapy)	Discontinue bevacizumab permanently.
Grade 3-4	Discontinue bevacizumab permanently.

Venous Thrombosis (Bevacizumab – Cohort 1 only)

Event	Bevacizumab

Grade 3 OR asymptomatic Grade 4	• Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 14 days, bevacizumab should be held until the full-dose anticoagulation period is over.
	• If the planned duration of full-dose anticoagulation is >14 days, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** all of the criteria below are met:
	  • The patient must have an in-range INR (usually 2-3) on a stable dose of warfarin, or on stable dose of heparin prior to restarting bevacizumab.
	  • The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major arteries or other conditions)
	  • The patient must not have had hemorrhagic events while on study
	• If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab

Grade 4	Discontinue bevacizumab permanently.

Proteinuria (Bevacizumab- Cohort 1 only)

Event	Bevacizumab
Grade 3 (UPC ≥ 3.5)	Hold drug until UPC < 3.5. If therapy is held for > 2 months due to proteinuria, discontinue drug permanently.
Nephrotic syndrome	Manage per standard of care. Discontinue drug permanently.

Skin Toxicities (hydroxychloroquine)

- Rash should be assessed as soon as possible to evaluate for possible rare side effects
- Sun protective measures should be encouraged
- If Grade =2, hold drug until rash has resolved to Grade 1 or less and resume at previous dose. If rash then worsens to > Grade 1, hold drug until rash resolved to grade 1 or less and resume at 50% dose.
- If Grade ≥ 3, discontinue drug permanently and manage according to standard of care.

Myopathy (hydroxychloroquine)

- If Grade = 2, hold drug until symptoms resolved to Grade 1 or less and resume at previous dose. If symptoms worsen to > Grade 1, hold drug until symptoms resolved to grade 1 or less and resume at 50% dose.
- If grade ≥ 3, discontinue drug permanently and manage according to standard of care.

Ocular Reactions (hydroxychloroquine)

- Any change in vision or any new visual symptoms (other than blurred vision, ≤ Grade 1) should result in holding drug until evaluation by an opthalmologist. Any findings attributable to drug will result in permanent discontinuation of drug. Management of symptoms should be per standard of care.

Other

- Any grade arterial thrombosis will result in permanent discontinuation of bevacizumab.
- Wound dehiscence requiring medical or surgical therapy will result in discontinuation of bevacizumab.
- Any Grade 3 or 4 congestive heart failure will result in discontinuation of bevacizumab.
- For Grade 3 AE attributable to bevacizumab and not listed above:
  - Hold bevacizumab until symptoms resolve to < Grade 1
  - If treatment delay is >14 days due to toxicity, discontinue bevacizumab
- For Grade 4 AE attributable to bevacizumab and not listed above:
  - Discontinue bevacizumab
  - **Upon consultation with the PI,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to < Grade 1 and unlikely to recur with retreatment.
- Bevacizumab should be held in patients with symptoms/signs suggestive of Reversible Posterior Leukoencephalopathy Syndrome (RPLS), pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.

7.6 Concomitant Medications

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed. All concomitant medications must be documented in the patient's medical records.

Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or hydroxychloroquine, drugs known to interact with the same CYP450 isoenzymes as hydroxychloroquine should be used with caution.

Medications known to have significant interactions with hydroxychloroquine:

Digoxin: Concurrent digoxin and hydroxychloroquine therapy has been reported to result in increased serum digoxin concentrations. Patients that take digoxin while on this study must monitor digoxin levels.

Metoprolol: Concurrent use of metoprolol, a CYP2D6 enzyme substrate, and hydroxychloroquine, a potent CYP2D6 enzyme inhibitor, may increase metoprolol exposure. Use caution when metoprolol is administered concomitantly with hydroxychloroquine, and monitor closely for metoprolol adverse effects (such as bradycardia).

Aurothioglucose: The concurrent use of aurothioglucose and antimalarial agents is *contraindicated.* Both aurothioglucose and antimalarial agents are capable of inducing blood dyscrasias, and concurrent use might result in an additive risk of this effect

7.7 Supportive Care Guidelines

All supportive measures consistent with optimal patient care will be given throughout the study. The clinical tolerance of the patients, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment. If treatment is discontinued due to any toxicity, the patient must be followed to monitor duration of toxicity, response and time to progression or survival and initiation of any new systemic therapy.

Recombinant erythropoietin may be administered for symptomatic and/or progressive $\geq$ Grade 2 anemia per the investigator's discretion and should be used as per approved prescribing information. Dosing recommendations for target hemoglobin must be followed. Alternative methods for managing hemoglobin, such as transfusions may be considered when medically appropriate.

Colony stimulating factors (filgrastim, pegfilgrastim, GM-CSF) should only be used if a neutropenic complication occurs after the first cycle despite dose reduction. If colony-stimulating factors are used, they must be used in accordance with the American Society of Clinical Oncology (ASCO) guidelines.

8. Toxicity Monitoring and Adverse Event Reporting

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle the treating physician will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. Adverse events will be recorded on electronic case report forms in accordance with a study-specific data capture plan.

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.1 Adverse Event Reporting Requirements

An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy.

All "unexpected" (defined below) and/or "serious" (defined below) adverse events occurring [redacted] event. Copies of each report sent to the IRB will be kept in the study regulatory file.

In addition to reporting to the local IRB, reporting to external bodies such as industry and/or the FDA may be required.

[redacted]

Reporting SAEs using commercially available drugs:

In addition, any unexpected (*not listed in the package insert*) serious adverse events that are associated (definitely, probably or possibly related) with the use of carboplatin, paclitaxel, bevacizumab or hydroxychloroquine, must be reported to the FDA within 10 business days using a FDA Form MedWatch 3500 form http://www.fda.gov/medwatch/safety/3500.pdf (fax # 1-800-FDA-0178).

8.2 Definition of Serious Adverse Events (SAEs)

A serious adverse event (experience) is one occurring at any dose level that results in any of the following outcomes:

- Death
- Life-threatening- immediate risk of death from the reaction.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent one of the outcomes listed in this definition.

The definition of serious adverse event (experience) also includes *important medical events*. Medical and scientific judgment will be exercised in deciding whether expedited reporting is

appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

The admission results in a hospital stay of less than 12 hours.

OR

The admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study).

OR

The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

8.3 Definition of Related

There is a reasonable possibility that the drug caused the adverse experience. That is, the event is judged by the investigator to be possibly, probably or definitely related to the treatment.

8.4 Definition of Unexpected

Any adverse drug experience and/or specificity, that is not included in the current investigator's brochure and/or package insert.

9. Treatment Evaluation/Criteria for Response

For the purposes of this study, patients should be reevaluated for response following every 2 cycles of therapy during the first 6 cycles. In addition to baseline scan(s), confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

[redacted]

9.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.2 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

9.3 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response. There may be occasions when progressive disease is suspected but cannot be fully characterized. In these cases the treating physician may decide to continue treatment for one or two cycles before reassessment, if he/she feels it is in the patients' best interest and the patient agrees to continue treatment.

9.4 Non-Target Lesions

All other lesions (or sites of disease) will be identified as non-target lesions and will be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

9.5 Guidelines for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique will be used whenever possible to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

9.5.1 Clinical lesions- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion.

9.5.2 Chest x-ray- Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

9.5.3 Conventional CT and MRI- These techniques will be performed with cuts of 10

mm or less in slice thickness contiguously. Spiral CT will be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

9.5.4 Ultrasound (US)- Because one of the endpoints of the study is objective response evaluation, US will not be used to measure tumor lesions. US might be used, at the discretion of the investigator, to confirm the complete disappearance of superficial lesions assessed by clinical examination.

9.5.6 Tumor markers- Tumor markers alone will not be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.5.7 Cytology, histology- These techniques may be used to differentiate between partial responses (PR) and complete responses (CR) if necessary and determined by the investigator. Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.6 Response Criteria

9.6.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

9.6.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and *normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.
Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the investigator will prevail.	

*Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.6.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Notes:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort will be made to document the objective progression.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination. The residual lesion will be investigated (fine needle aspirate/biopsy if possible) before confirming the complete response status.

9.7 Confirmatory Measurement/Duration of Response

9.7.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry after a minimum interval of 2 cycles of treatment.

9.7.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

9.7.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10. Removal of Patients from Study/Off Study Criteria

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

a) Disease progression/relapse during active treatment,
b) Intercurrent illness that prevents further administration of treatment,
c) Unacceptable adverse event(s).
d) In the event of any drug-related life-threatening toxicity or laboratory abnormality the patient will be withdrawn from further treatment,
e) Patient decides to withdraw from the study,
f) Noncompliance with treatment plan,
g) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
h) Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the Principal Investigator.