A Phase II Trial of High-Dose Ascorbate in Stage IV Non-Small Cell Lung Cancer

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SUMMARY OF CHANGES

Section	Change
07 November 2018	
Cover	Updated date, version
3.1.2	Clarified patient base for those who have received prior therapy with curative intent.
3.2.2	Clarified PDL-1 expression requirements
5.1	Inserted, "(except transient increase in blood pressure)" for clarification.
5.6.2	Change of follow-up from active to passive through chart review and following standard-of-care. This is for scheduling convenience for further systemic therapy or to release to local care for palliation.
6.5	Harmonized follow-up requirements to section 5.6.2 for passive follow-up through standard of care.
6.6.2	Inserted, "stable," for further clarification.
11 [Study Calendar]	Updated follow-up per sections 5.6.2 and 6.5
04 January 2018	
Schema	inserted iron panel and ferritin as baseline assessments
5.3.6	deleted extra (i.e. empty) bullet-point
5.3.8	adjusted schedule to ± 7 calendar days to mirror standard of care and enable adjustments for clinical scheduling
6.1	inserted 6.1.13 listing an iron panel (iron, transferrin, TIBC, and % saturation) as a baseline lab
6.1	inserted 6.1.14, listing ferritin as a baseline lab
6.2	inserted 6.2.14, listing the iron panel and ferritin as required labs for cycles 1 and 3 only.
11 (Study calendar)	inserted iron panel and ferritin line item, inserted footnote *s.*
Appendix C	Updated monitoring plan for consistency with data and safety monitoring plan approved by NCI for UIOWA's cancer center.
Appendix C	Added risk of gout or gout-like symptoms as possible side effect
04 April 2017	
Cover	Updated date, version
7.3.1	Updated to include McGuff Pharmaceuticals, Inc as the preferred supplier
7.3.2	Inserted text regarding Ascor L-500, renumbered subsequent text accordingly.

January 08, 2017

Cover	Updated personnel, date, version
Schema	Updated information to be consistent with section 3.1
1.2	Updated secondary objectives to include stage IIIB NSCLC
3.1.5	Clarified creatinine limit with regard to ULN, for consistency with CTCAE v4.03
3.1.5	Clarified T.Bilirubin limit with regard to ULN, for consistency with CTCAE v4.03
3.1.7	Inserted criterion for patients who have received prior neo-adjuvant, adjuvant, chemoradiation, or radiation therapy with curative intent; renumbered Inclusion Criteria accordingly.
3.2.1	Clarified EGFR mutations (i.e., sensitizing) and edited sentence for clarity.
3.2.2	Inserted criterion for PD-L1 expression in response to updated approved therapeutic options; renumbered Exclusion Criteria accordingly.
3.2.9	Clarified other invasive malignancies as excluded if they are active.
5.3.2	Inserted section on body weight, calling out C1D1 as baseline for chemotherapy calculations; change weight if >10% change. Renumbered accordingly.
5.3.3	Inserted section on body height, calling out C1D1 as baseline for chemotherapy dose calculations. Renumbered accordingly.
5.3.5	Inserted reference to sections 5.3.2, 5.3.3
5.3.6	Inserted reference to sections 5.3.2, 5.3.3
5.4.10	Inserted section to address palliative radiotherapy, for those patients requiring radiation therapy to alleviate pain or secondary symptoms of their malignancy.
5.7	Changed ‘study’ to ‘treatment’ to clarify that those participants who have received 2 cycles of therapy will have life-long follow-up.
12.1	Inserted (Primary End-Point) for clarity.
Appendix: Eligibility checklist	Harmonized with protocol section 3, Eligibility Criteria
Appendix: Monitoring worksheets	Harmonized with protocol

August 09, 2016

Cover	Updated date, version
Schema	Inserted information regarding health-related quality of life.
9: Study calendar	Inserted row for health-related quality of life.

10: Correlative studies	Added health-related quality of life information to establish patient-reported outcomes for this trial.
Eligibility checklist	Updated amendment; corrected ‘conception’ to ‘contraception’

March 03, 2016

Cover	Updated date, version
5.3.4	Added bullet to address use of current weight for carboplatin dosing
6.2.7	Deleted ‘dry mouth’ as required assessment; renumbered accordingly
6.5.1	Inserted, ‘[this sample should be drawn regardless of additional therapy; can be drawn subsequent cycles D1 if within window]’ for clarification
Study calendar: ROS	Marked ROS as required at follow-up, for consistency with text of protocol
Study calendar: *b*	updated footnote for consistency with protocol section 5.8
Study calendar: *c*	updated footnote for consistency with protocol section 5.6.2
Study calendar: *f*	updated footnote for consistency with protocol sections 5.3.3 and 5.3.4
Appendix C: Eligibility checklist	updated to be consistent with protocol section 3
Appendix D: monitoring templates	updated to remove ‘dry mouth’ as evaluated toxicity (C1, C2, C3, C4)

January 15, 2016

Cover	Updated personnel, date, version
Schema	Added ‘and uric acid within 21 days of D1’ to Baseline assessments.
3.2.1	Clarified allowance for inadequate tissue sample, inconclusive assessment, or tumor not amendable to biopsy as potential for patient inclusion.
3.2.2	Inserted exclusion for warfarin therapy due to its theorized interaction with ascorbate; renumbered accordingly.
5.2.1	Inserted ‘/ infusion for therapy’ for clarity.
5.3.1	Inserted text to address subjects who fall outside of start window.
5.3.6	Inserted, “May be adjusted ± 2 days for scheduling.” for consistency with UIHC standard practice
5.4.2	Added ‘(CT)’ and ‘for CT’ for clarification so statement reads, “Imaging Contrast (CT). Imaging contrast for CT should not be….”
5.4.3	Inserted text on Imaging Contrast (MRI) for clarification. Renumbered accordingly.
5.4.5	Inserted text on theorized interaction with warfarin (coumadin).

5.6.2	Changed follow-up target to 28d from 21d; changed window from '+ 10 calendar days' to '±7 calendar days.' Changed first follow-up appointment from '3 months' to '2-4 months' to accommodate chemotherapy schedules post-study.
5.8.1	Changed follow-up target to 28d from 21d; changed window from '+ 10 calendar days' to '±7 calendar days.' This is to accommodate standard schedules for chemotherapy for scheduling convenience.
6.5	Changed follow-up target to 28d from 21d; changed window from '+ 10 calendar days' to '±7 calendar days.' This is to accommodate standard schedules for chemotherapy for scheduling convenience.
7.3.2	Inserted 'CT' for clarification regarding imaging contrast
7.3.4	Inserted 'CT' for clarification regarding imaging contrast
8.1	Corrected 'administer' to 'consider / per physician discretion' to allow for individual medication variance per UIHC standard therapy
8.4.2, 8.4.3	Moved 'Dose Delays' from section 8.4.3 to section 8.4.2. Renumbered accordingly.
8.4.2	Changed text to allow up to a 3 week delay in ascorbate administration. Removed qualifiers for dose delay (e.g., holidays, inclement weather).
11 [study calendar]	Inserted 'Uric Acid' and 'baseline' (for timeframe), consistent with protocol requirements.
11 [study calendar]	Regarding Footnote 'n' – inserted 'CT' to clarify contrast contraindication
Appendix C	Updated eligibility checklist for consistency with section 3.0
Appendix C	Inserted 'CT' in Imaging Contrast for consistency
Appendix D	Inserted 'Uric Acid' into Baseline Assessment worksheet
Appendix D	Removed 'Chills' from worksheets, moved 'History/Physical' to open space. Chills are not actively captured as an adverse event for this trial.

April 04, 2015

Cover	Updated date, version
Schema (page)	Added, "blood for research obtained before 15g test" under Baseline assessments.
Schema (page)	Corrected creatinine eligibility to less than or equal to 1.5 mg/dL
6.1	Clarified window for pre-treatment assessments.
6.2	Deleted, "On cycle day 1, collect the following information." Every attempt should be made to have these assessments done day 1 but they can be performed on another day as decided by the research team.
6.2	Clarified blood sampling for ascorbate and ROS testing. Added ROS testing for cycle day 2.
6.3	Removed temperature and heart rate as it is no longer required as a routine safety assessment per the sponsor and medical monitor. Should be captured if indicated clinically.

6.3	Clarified window for pre- and post-infusion BP/HR assessments
10	Clarified blood sampling schedule for consistency.
11	Study calendar edited for clarity (screen v. baseline)
Throughout	Removed space between '°' and 'F,' or 'C'
Appendix	Corrected monitoring sheets to be consistent with section 6.3

January 26, 2015

Cover	Updated date, version
5.3.4	Updated GFR maximum to FDA recommendations of 125 ml/min for all patients.
6.1.9	Added uric acid level at baseline. Renumbered accordingly.
6.1.10	Added, "Draw in a 4mL green-top Na Heparin tube."
8.3.5	Updated GFR maximum to FDA recommendations of 125 ml/min for all patients.
Appendix B	Updated CUP3A4 interaction tables, provided by UIHC drug services

December 22, 2014

Cover	Updated study personnel, date, version

November 25, 2014

Cover	Updated study personnel, date, version
iii	Deleted "uric acid" from the eligibility table
3.1.5	Removed uric acid from screening labs
3.2.2	Changed 'known' to 'active' and added 'within 1 week of screening' to criterion so that it reads, "Active hemoptysis within 1 week of screening."
5.1	Changed "Start up to" to "Can be given any time through" to clarify when the ascorbate test dose may be administered.
5.2.5	Duration corrected in opening sentence to 4 cycles, from 2. Inserted 'chemotherapy' for clarification.
Table 1	Added "for injection only" to clarify type of sterile water allowed.
5.3.7	Duration corrected from 2 cycles to 4 cycles.
5.8	Added, "End-of-Study does not apply to subjects who complete all 4 cycles of chemotherapy."
5.9	Corrected "adjuvant" to "additional"
6.2.8	Added "(may be done up to 1 week before cycle day 1)"
6.2.9	Added "may be done up to 1 week before cycle day 1)"

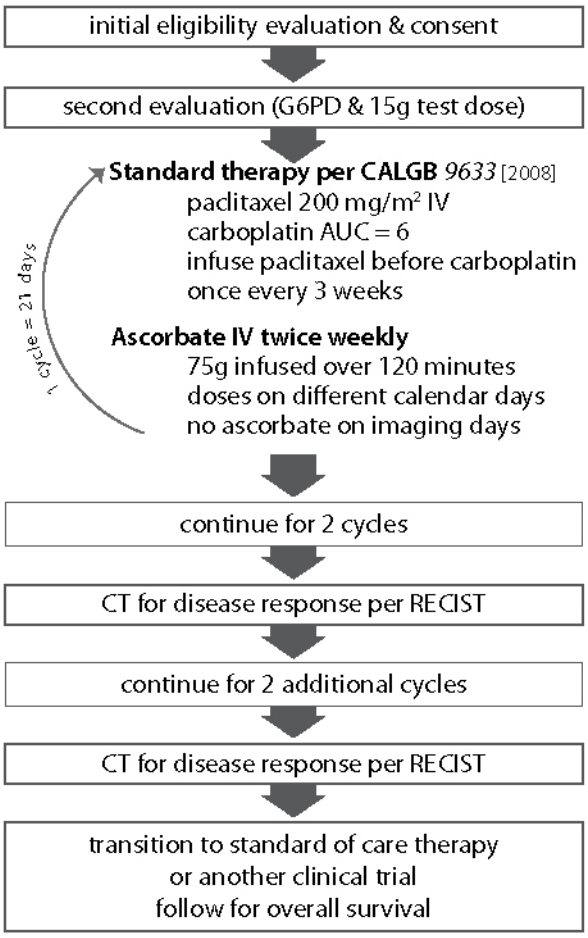
6.2	Added “Once during the chemotherapy cycle, collect the following information:” between sub-section 6.2.9 and 6.2.10 to provide clarification that the ascorbate levels should just be drawn once per cycle but not necessarily on cycle day 1.
6.2.12	Added “Test prior to infusion and at the end of infusion (i.e., at the same time as the blood draws for ascorbate levels)” to further clarify when these tests should be performed.
6.3	Changed infusion assessments from “each hour” to “in the interim as clinically indicated.”
6.4	Added “CT imaging with contrast cannot be performed on the same day as an ascorbate infusion.”
6.5.2	Inserted “(follow-up #1, only)” because a CBC w/differential will only be required for research purposes at the first follow-up visit.
6.5.3	Inserted “(follow-up #1, only)” because a CBC w/differential will only be required for research purposes at the first follow-up visit.
6.5.5	Added section to specify that labs drawn for standard of care, or other purposes, may be reviewed to retrospectively assess long-term treatment effects and adverse events.
6.5.6	Added section to specify that medical information may be reviewed to retrospectively assess long-term treatment effects and adverse events. Renumbered subsequent sections appropriately.
9.1.2	Inserted, “Grading may be done by any licensed medical personnel (e.g., research nurse, treating physician, etc.) with final determination made by the principal investigator” to provide clarification over standard procedures.
9.1.3	Inserted, “grade 3 or greater” for section to read, “Initial attribution of ascorbate to a grade 3 or greater event may be assigned by *any* licensed medical personnel…” to clarify that attributions will be made only for grade 3 or greater CTCAE events *unless* lesser events are unexpected.
9.1.3	Inserted, “CTCAE grade 2 and lesser events do not require attribution *unless* the event is unexpected (i.e., not related to chemotherapy, tumor, or previously diagnosed underlying condition).”
Table 2	Deleted serious adverse event definition as it is listed prior to table 2.
Section 11: Study Calendar	Inserted footnote ‘g’ for *comprehensive metabolic panel* ‘d1’ and clarified that footnote to allow labs drawn up to, and including, a week prior
Section 11: Study Calendar	Inserted footnote ‘c’ for *comprehensive metabolic panel* ‘F/U’ and clarified that footnote to specify labs are only drawn at the first FU appointment
Section 11: Study Calendar	Inserted footnote ‘c’ for *CBC w/diff* ‘F/U’ and clarified that footnote to specify labs are only drawn at the first FU appointment
Section 11: Study Calendar	Clarified footnote ‘d’ for *history physical* that the physical may be done up to, and including, 1 week before day 1 of chemotherapy.

Section 11: Study Calendar	Clarified footnote ‘i’ to read blood specimens to be drawn once per cycle, and that a finger-stick glucometer will also be used to obtain ascorbate levels.
Section 11: Study Calendar	Added to footnote ‘n’ “DO NOT schedule on days with ascorbate infusions. Ascorbate and contrast are contraindicated.
Appendix D: recommended monitoring worksheets	Updated monitoring worksheets to be consistent with changes to protocol.

September 2, 2014

Section	Change
N/A	Initial submission received by FDA; pre-release v0.13

SCHEMA



Screening. Order G6PD post-consent. Subject must be able to tolerate one 15g test infusion of ascorbate.

Baseline assessments. Fatigue, neuropathy, infection, nausea, vomiting, and pain (headache) iron panel, ferritin, and uric acid within 21 days of D1. Blood for research obtained before 15g test.

Health related quality of life. At baseline, then day 1 of cycles 2, 3, & 4, then before the last ascorbate infusion.

Adverse events. Screened cycle D1 against case report form. Onset and severity of events to be quantified.

End of active participation. Active participation ends at the CT scan after 4 cycles of therapy.

Follow-up. Minimum 21d post-dose; survival through chart review.

Enrollment. Targeted enrollment of 37 participants for phase II evaluation.

Selected Patient Eligibility Requirements (Section 3.1)

- Ability to understand and the willingness to sign a written informed consent document
- Diagnosis of stage IIIB, IV, or recurrent NSCLC
- Indication for chemotherapy
- ECOG 0-2
- No glucose-6-phosphatase dehydrogenase deficiency
- No known active invasive malignancy

ANC	$\geq$ 1,500 mm^3
Platelets	$\geq$ 100,000/mm^3
Hemoglobin	$\geq$ 8 g/dL
Bilirubin, total	$\leq$ 1.5 x ULN
AST	$\leq$ 3x ULN
ALT	$\leq$ 3x ULN
Creatinine	$\leq$ 1.5 x ULN

TABLE OF CONTENTS

1. OBJECTIVES

1.1. Primary Objectives

1.1.1. Determine initial tumor response per RECIST 1.1 criteria.

1.2. Secondary Objectives

1.2.1. Determine the median time to progression for patients with stage IIIB/IV NSCLC treated with high dose ascorbate when administered concurrently with carboplatin and paclitaxel.

1.2.2. Determine the progression free survival and overall survival of patients with stage IIIB/IV NSCLC treated with high dose ascorbate when administered concurrently with carboplatin and paclitaxel.

1.2.3. Determine the incidence of toxicity with the 3 drug combination of paclitaxel, carboplatin and ascorbate

2. BACKGROUND

2.1. Stage IV Non-Small Cell Lung Cancer (NSCLC) and its current therapy

Lung cancer is the number one cause of cancer related mortality worldwide and results in approximately 1.2 million deaths per year.[1,2] Approximately 75% of all lung cancers are classified as non-small cell lung cancer (NSCLC).[1] For patients with resectable disease (20% of all lung cancers) the cure rates are approximately 40-70%.[3,4] Unfortunately, the majority of patients with NSCLC, however, present with advanced disease (stage IIIB or IV)[5]. The standard treatment for patients with metastatic lung cancer is chemotherapy. Despite advances in new chemotherapy approaches, there has been little improvement in patient outcomes.

The current standard of care first line chemotherapy treatment of advanced stage NSCLC without known activating gene mutation is platinum doublet. In a cornerstone randomized trial by Schiller et al,[6] the regimen of carboplatin and paclitaxel showed a better toxicity profile and was not inferior to the cisplatin containing regimens. However, this trial showed a response rate to chemotherapy of only 20% and a median overall survival of 7.9 months. In another trial, ECOG 4599,[7] adding bevacizumab, a vascular endothelial growth factor inhibitor, to carboplatin and paclitaxel improved the median overall survival for advanced stage NSCLC to 12.3 months, however, this combination resulted in more toxicity, including fatal bleedings. The major breakthroughs in NSCLC treatment in the last decade came from developing novel therapies that target specific gene alterations in a small subset of NSCLC patients. This include EGFR[8] and ALK[9] tyrosine kinase inhibitors (TKIs) which resulted in dramatic tumor responses and significant prolongation of survival. Although targeted therapy had proven to be very effective as an initial treatment in the right setting, it is limited by the small frequency of these gene abnormalities, the inevitable emergence of cancer resistance to the TKIs and the rapid progression upon acquiring resistance. These studies highlight the dismal prognosis of patients with advanced stage NSCLC despite undergoing aggressive therapy. Complementary approaches that enhance chemotherapy and are well tolerated are urgently needed. One promising and innovative approach that exploits the fundamental metabolic differences between cancer cells and normal cells is high dose or pharmacological ascorbate.

2.1.1. Ascorbate as an anti-tumor agent.

Ascorbate (ascorbic acid, vitamin C, AscH) is one of the early unorthodox therapies for cancer, based on two unsupported hypotheses. McCormick postulated that ascorbate protects against cancer by increasing collagen synthesis,[10,11] while Cameron hypothesized that

ascorbate could have anti-cancer action by inhibiting hyaluronidase and thereby prevent cancer spread.[12] These hypotheses were subsequently promoted by Cameron and Pauling.[13,14] Cameron and Campbell initially published case reports of 50 patients; some seemed to have benefited from high dose ascorbate.[15] Cameron and Pauling then published results of 100 patients with terminal cancer that were given intravenous ascorbate.[16] The ascorbate-treated patients were compared to 1000 retrospective controls with similar disease. Patients who received ascorbate survived on average 300 days longer than controls.[14,16] A prospective study was then conducted that randomized patients to ascorbate treatment or palliative therapy. Treated patients had a median survival of 343 days *vs*. 180 days for controls.[17] Smaller studies have also reported benefits of ascorbate.[18,19]

To test "definitively" whether ascorbate was effective, Moertel conducted two randomized placebo-controlled studies randomized to oral ascorbate; neither study showed benefit.[20,21] Subsequently, ascorbate therapy was considered ineffective. However, it was not recognized until approximately 15 years later that oral and intravenous ascorbate have strikingly different pharmacokinetics.[22,23] This difference in the administration route is key. Cameron gave patients ascorbate intravenously as well as orally, while Moertel's patients received only oral ascorbate. Thus, the issue of ascorbate in cancer treatment needs to be re-examined.

The evidence for use of ascorbate in cancer treatment falls into two categories: clinical data on dose concentration relationships and laboratory data describing potential cell toxicity with high concentrations of ascorbate *in vitro*. Clinical data show that when ascorbate is given orally, fasting plasma concentrations are tightly controlled at < 100 μM.[24] As doses exceed 200 mg, absorption decreases, urine excretion increases and ascorbate bioavailability is reduced.[22,24] In contrast, when 1.25 grams of ascorbate are administered intravenously, concentrations as high as 1 mM are achieved. Some clinicians have infused more than 10 grams of ascorbate in cancer patients and achieved plasma concentrations of 1 to 5 mM.[25] Thus, it is clear that intravenous administration of ascorbate can yield very high plasma levels, while oral treatment does not.

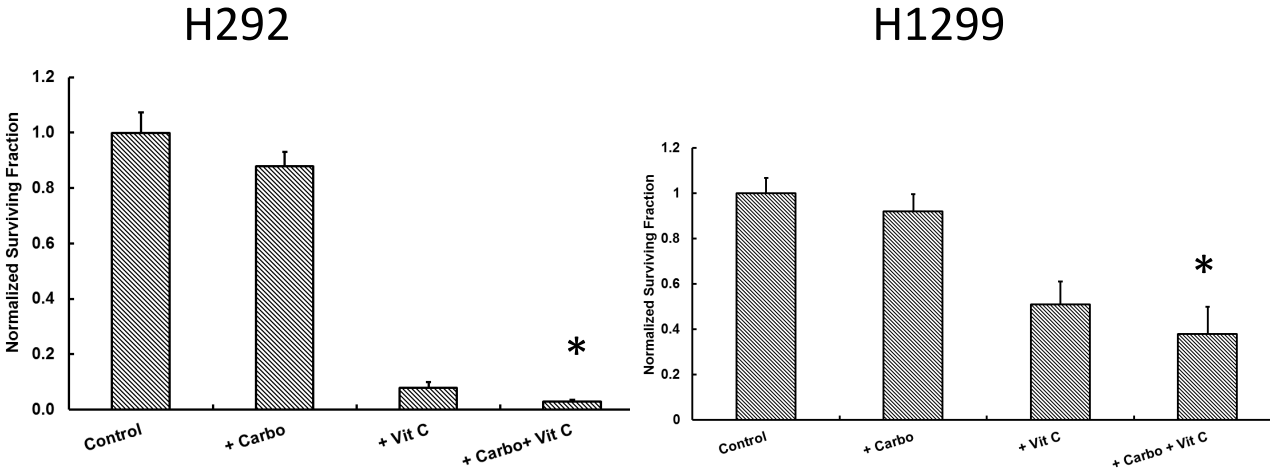


Figure 1. Pharmacological levels of ascorbate enhance NSCLC cell lines, H292 and H1299, sensitivity to chemotherapy. Cell survival was determined using the clonogenic cell survival assay. Cell lines were treated with ascorbate (0.5 mM) and carboplatin (10μm) for 1h. Clonogenic cell survival was decreased in both cell lines when treated with carboplatin and ascorbate. Means, n = 3.*P < 0.05 vs. carboplatin alone.

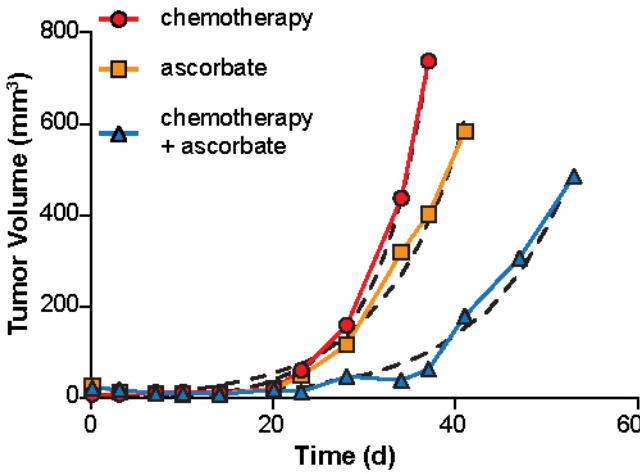


Figure 2. NSCLC H1299 tumor volume averages. Tumor volume measurements of chemotherapy treated, ascorbate treated, and chemotherapy + ascorbate treated mice. Pharmacological ascorbate significantly decreased tumor growth relative to carboplatin + radiation therapy. $p = 0.0168$.

Pharmacologic ascorbate concentrations have been shown to selectively kill many cancer cell types. Chen *et al*. measured cell death in 10 cancer and 4 normal cell types using 1-hour exposures to pharmacological ascorbate.[26] Normal cells were unaffected by 20 mM ascorbate whereas 5 cancer cell lines had EC_{50} values of < 4 mM, a concentration achievable by intravenous administration. In addition, cell death was independent of metal chelators, but dependent on formation of H_2O_2.[27] H_2O_2 generation was dependent on ascorbate concentration, incubation time; [H_2O_2] displayed a linear increase with [AscH] and it increased as a quadratic function of ascorbate radical, ascorbate being an electron donor to O_2 to form superoxide and, eventually, H_2O_2.

When ascorbate is infused intravenously the resulting pharmacologic concentration will distribute rapidly into the extracellular water space.[28] *In vivo*, Chen and colleagues demonstrated that intravenous injection of ascorbate (0.25-0.5 mg/g body weight) increased baseline concentrations of ascorbate in the blood and extracellular fluid to > 8 mM as well as increased formation of H_2O_2.[29] More recent studies have demonstrated that intraperitoneal doses of 4 g/kg ascorbate resulted in blood concentrations of 40 mM; tumor extracellular fluid increased to peaks of 20 mM for up to 3 hours.[24]

Our data demonstrate that pharmacologic doses of ascorbate are cytotoxic to NSCLC cell lines and that it enhances chemotherapy sensitivity *in vitro* (Figure 1). Additionally, intraperitoneal administration of high dose ascorbate in combination with carboplatin and radiation inhibits orthotopic NSCLC growth and decreases tumor size in mice without causing an associated toxicity (Figure 2). Combined, these studies provide a foundation for pursuing pharmacologic ascorbate as a prooxidant agent in cancer therapy and specifically in NSCLC

Ascorbate-mediated cell death has been shown to be due to H_2O_2 generation, *via* ascorbate radical formation, with ascorbate as the electron donor.[26,27,29] When ascorbate is infused intravenously the resulting pharmacologic concentration distributes rapidly in the extracellular water space.[29] Thus, pharmacologic ascorbate concentrations in media, as a surrogate for extracellular fluid, should generate ascorbate radical and H_2O_2. In contrast, the same pharmacologic ascorbate concentrations in whole blood generate little detectable ascorbate radical and no detectable H_2O_2.[21] This can be accounted for by efficient and redundant H_2O_2 catabolic pathways in whole blood relative to those in media or extracellular fluid. Thus, ascorbic acid administered intravenously in pharmacologic concentrations may serve as a pro-drug for H_2O_2 delivery to the extracellular milieu, but without H_2O_2 accumulation in blood.

In a Phase I trial of intravenous ascorbic acid in patients with advanced pancreatic cancer conducted at the University of Iowa Hospitals and Clinics, adverse events and toxicity were minimal at all dose levels. The high-dose intravenous ascorbic acid was well tolerated when administered to patients. Ascorbic acid concentrations reached up to 25 mmol/L in patients

who received ascorbic acid of 1.5 g/kg. Of the 24 patients in the study, only 4 recorded minor adverse events including headache, dizziness and diarrhea.[30]

2.2. Ascorbate Preliminary Data

2.2.1. Pre-clinical (*in vitro).*

Figure 1 demonstrates that pharmacological ascorbate enhances sensitivity of NSCLC cell lines, H1299 and H292 to carboplatin. Cells were treated with ascorbate (0.5mM) and carboplatin (10μM) for one hour. Cell survival was determined by clonogenic cell survival assay. These results support the hypothesis that ascorbate enhances radiation induced cell killing of NSCLC cells.

2.2.2. Pre-clinical (*in vivo*)

To determine if treatment of established NSCLC tumors in a xenograft model with ascorbate would inhibit growth, H292 tumor cells (2×10^6) were delivered subcutaneously into the flank region of nude mice and allowed to grow until they reached 3 mm in greatest dimension (~ 10 days), at which time they were randomly assigned to a treatment group. This was defined as day 1 of the experiment. The animals were randomized to receive either: sham treatment (control), ascorbate (4 g/kg) i.p. given to mice every day for two weeks, and ascorbate with radiation (12Gy in 2 fx) administered during the middle of ascorbate therapy in select mice. Data from Dr. Mark Levine's laboratory have demonstrated that 4 g/kg i.p. ascorbate resulted in blood concentration from baseline of 40 μM to peaks of 40 mM while tumor extracellular fluid increased to peaks of 20 mM for up to 3 hours [personal communication].[22] The primary outcomes of interest were tumor growth over time and the potential toxicity of combining carboplatin, radiation and pharmacological ascorbate. Tumor size (mm^3) was periodically measured via calipers throughout the experiments, resulting in repeated measurements across time for each mouse. Linear mixed effects regression models were used to estimate and compare the group-specific tumor growth curves. The observed tumor volumes for all mice are plotted over time in Figure 2.

2.2.3. Clinical trial data:

Combining carboplatin and paclitaxel with high dose ascorbate was studied in a phase I clinical trial in ovarian cancer [31]. This combination was shown to significantly decrease the adverse effects from chemotherapy. The sample size was too small to show increased efficacy of this combination.

2.3. Rationale

Metastatic NSCLC is the most common stage of NSCLC with a poor overall survival. We propose to investigate an entirely new approach, using pharmacological ascorbate, combined with chemotherapy to treat NSCLC. Intravenous ascorbate (*i.e.,* ascorbic acid, vitamin C), but not oral ascorbate, produces high plasma concentrations, which are in the range that can be cytotoxic to tumor cells. Though ascorbate has been utilized in cancer therapy, few studies have investigated intravenous delivery of ascorbate. Preliminary studies from our group have demonstrated that ascorbate induces cytotoxicity in NSCLC cells. Phase I clinical trial showed the combination of high dose ascorbate with carboplatin and paclitaxel in ovarian cancer improved the toxicity profile associated with this chemotherapy regimen. Proceeding to a phase II clinical trial to study efficacy of carboplatin and paclitaxel with high dose ascorbic acid as a first line treatment for stage IV NSCLC patients is a logical next step in evaluation.

3. SUBJECT SELECTION

3.1. Eligibility Criteria

3.1.1. Patients must have newly diagnosed histologically or cytologically confirmed NSCLC, staged IIIB or IV, for which they have not received first-line cytotoxic chemotherapy (first-line EGFR inhibitors or ALK inhibitors are allowed given disease progression).

3.1.2. Patient with recurrent disease for whom palliative intent systemic therapy is indicated are also eligible regardless of stage of their disease. Patients who received prior neo-adjuvant, adjuvant chemotherapy or chemo-radiation or radiation with curative intent for non-metastatic NSCLC must have experienced a treatment-free interval of at least 6 months from signing the informed consent since the last chemotherapy or chemo-radiation or radiation treatment/cycle. Patients developing recurrent disease while receiving consolidation immunotherapy after definitive chemo-radiation or surgery for whom palliative intent therapy is indicated will be eligible for the study as far as their last cycle of immunotherapy is 3 weeks from the day of consent (6 months' time-line is not applicable to consolidation immunotherapy).

3.1.3. Patients with CNS metastasis will be allowed on the study if the metastasis is treated, no clinical signs of metastasis progression following treatment, and the patient is off steroids for at least 3 days (only if steroids are prescribed specifically for brain metastasis).

3.1.4. Age $\geq$ 18 years

3.1.5. ECOG performance status 0-2 (see Appendix A).

3.1.6. Screening labs should be within the following limits and obtained within 21 days of cycle 1, day 1:

- Absolute neutrophil count (ANC) $\geq$ 1500 cells per mm^3
- Platelets $\geq$ 100,000 per mm^3
- Hemoglobin $\geq$ 8 g/dL
- Creatinine $\leq$ 1.5 x the institutional upper limit of normal
- Total bilirubin $\leq$ 1.5 x the institutional upper limit of normal
- ALT $\leq$ 3 times the institutional upper limit of normal
- AST $\leq$ 3 times the institutional upper limit of normal

3.1.7. Tolerate a 15g ascorbate infusion (screening dose).

3.1.8. Not pregnant. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while receiving study drug, she should inform her treating physician immediately. Pregnancy tests will be obtained per physician discretion.

3.1.9. Not breastfeeding.

3.1.10. Ability to understand and willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1. Known sensitizing EGFR mutations or ALK gene rearrangement as these patients will benefit from targeted oral tyrosine kinase inhibitors as a first line treatment. If patient's biopsy did not allow EGFR or ALK gene analysis (e.g., inconclusive, not

enough tissue, etc.), the patient is considered eligible for study. Enrollment on this clinical trial after progression on targeted therapy is allowed.

3.2.2. Patient with strong PD-L1 expression (≥ 50% of tumor cells expressing PD-L1 or tumor proportion score (TPS) ≥ 50%) will be excluded as they may derive more benefit from from immunotherapy. Patient's with unknown PD-L1 expression or when PD-L1 expression can't be determine due to insufficient tumor sample or other reasons will be eligible for this study. At progression or due to intolerable toxicity on immunotherapy, these patients will then be eligible for the study. Receiving warfarin therapy and cannot tolerate drug substitution.

3.2.3. Active hemoptysis within 1 week of screening (more than ½ teaspoon per day)

3.2.4. Actively receiving insulin at time of ascorbate infusion (unless an exception is granted by the IND sponsor, medical monitor, and the PI).

3.2.5. Leptomeningeal disease

3.2.6. G6PD (glucose-6-phosphate dehydrogenase) deficiency

3.2.7. Patients who are on the following drugs and cannot have a drug substitution: flecainide, methadone, amphetamines, quinidine, and chlorpropamide. High dose ascorbic acid may affect urine acidification and, as a result, may affect clearance rates of these drugs.

3.2.8. Patient with known active invasive malignancy other than NSCLC. .(Exceptions: non-melanoma skin cancer or carcinoma in-situ of the cervix or bladder)

3.2.9. Patients may not be receiving any other investigational agents with the intention to treat their cancer (imaging trials are acceptable).

3.2.10. Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.11. Known HIV-positive individuals. High-dose ascorbate acid is a known CYP450 3A4 inducer, which results in lower serum levels of antiretroviral drugs.[32]

3.3. Inclusion of Women and Minorities

Female and male patients of all ethnic groups will be eligible for treatment on this protocol.

4. REGISTRATION PROCEDURES

Once informed consent is obtained:

- Fax a copy of completed eligibility criteria to DSMC, labeled with subject ID and initials.
- Enter subject into the OnCore database of the Holden Comprehensive Cancer Center
- Scan the record of consent into the subject's medical record.
- Scan the G12 into the subject's medical record.

5. TREATMENT PLAN

Protocol should not supersede standard of care procedures for patient safety.

5.1. Post-consent Screening Procedures

If subjects fail the G6PD or test doses of ascorbate, they are considered a screen failure.

- G6PD test (off-site test, so draw immediately). If subject has a prior G6PD test, this can be used as G6PD levels do not fluctuate (i.e., there is no window for this test).
- Ascorbate initiation (one test dose of ascorbate): Can be given any time through the day

Table 1. Recommended Infusion Times for Pharmacological Ascorbate †

Ascorbate dose (500 mg / mL)	Total volume*	Osmolarity (mOsm/L)§	Infusion Time
15g (30 mL)	250 mL	681	30 minutes
75g (150 mL)	1000 mL	851.7	120 minutes

† Provided by Drug Information Center at the University of Iowa, July 2011

* Sterile water for injection only. Do not use D5W

§ Theoretical calculations provided by Drug Information Center; targeted osmolarity range is 500 – 900 mOsm/L

prior to chemotherapy with one 15-g infusion. Failure of the 15g test dose is defined as any toxicity ≥ CTCAE grade 3 (except transient increase in blood pressure) or a significant medical event (in the opinion of the principal investigators).

5.2. Concomitant Ascorbate (High-dose Ascorbic Acid) Infusions with Carboplatin and Paclitaxel

5.2.1. **Participant dose**. After completing a 15g test dose for screening, subjects will receive 75g / infusion for therapy. Dose modifications are not made for weight or body surface area.

5.2.2. **Administration**. Based on subject tolerance; infusion rate should not exceed 500 mL/hour without consulting with physician. Recommended infusions times are provided (Table 1) but may be adjusted for subject comfort. Changes in infusion rates should be recorded.

5.2.3. **Schedule**. Schedule two times weekly, must be on separate calendar days.

5.2.4. **Cycle**. Concomitant with carboplatin and paclitaxel, 21 day cycle.

5.2.5. **Duration.** Subjects will continue with therapy for 4 chemotherapy cycles or until one of the criterion for removal are met (Section 5.7). Patients with complete response, partial response or stable disease will continue for two more cycles of paclitaxel/carboplatin, ascorbate and another CT will be done to assess response after 4 cycles. After 4 cycles study therapy will be complete and maintenance therapy will be allowed in accordance with standard care.

5.2.6. **Dose modifications.** Provided in Section 8

5.3. Chemotherapy (paclitaxel / carboplatin regimen)

The carboplatin / paclitaxel regimen is administered following standard practice adopted at UIHC, based on the chemotherapy doses established by CALGB 9633.

5.3.1. **Initiation**. Within 21 days of signing the consent form. If a subject has a delay of therapy, the subject may be re-screened/re-consented for participation.

5.3.2. **Body weight:** C1D1 weight will be used for chemotherapy calculations unless there is a change of >10% from C1D1 weight

5.3.3. **Body height:** C1D1 height will be usedfor chemotherapy calculations.

5.3.4. **PACLITAXEL Premedications**. UIHC standard of care premedication procedures should be followed for chemotherapy administration. Thirty minutes before administering paclitaxel:

- dexamethasone 20 mg intravenously (IV)

- diphenhydramine, 25-50 mg orally
- famotidine, 20 mg orally
- antiemetic

5.3.5. **PACLITAXEL dose**. 200 mg/m^2 (sections 5.3.2, 5.3.3) over 3 hours continuous infusion. Paclitaxel must be administered prior to carboplatin.

5.3.6. **CARBOPLATIN dose.** AUC = 6 using the Cockcroft-Gault formula. Administered 6 mg/mL x min over 1 to 2 hours (sections 5.3.2, 5.3.3).

- **Creatinine adjustment.** If creatinine is <1 mg/dl, then the creatinine used for carboplatin dose calculation will be adjusted to 1 mg/dl.
- **BMI adjustment.** For patients with high BMI, the maximum allowed calculated creatinine clearance will be males at 125 ml/min and females at 125 ml/min.

5.3.7. **Administration**. Paclitaxel must be infused prior to carboplatin. Infuse per standard UIHC practices.

5.3.8. **Schedule**. Once every 21 days. May be adjusted ± 7 calendar days to allow for scheduling.

5.3.9. **Cycle**. A total of 4 cycles of paclitaxel/carboplatin will be administered for the purposes of this study.

5.3.10. **Antiemetics**. Use Zofran (ondansetron) with caution as this medication may interact with high-dose ascorbic acid, resulting in sub-efficacious levels of Zofran.

5.3.11. **Dose modifications.** Provided in Section 8.

5.4. General Concomitant Medication and Supportive Care Guidelines

5.4.1. **Prophylactic antibiotics for neutropenia**: To be considered by the treating physician for neutropenia. Ciprofloxacin 500 orally, twice daily, is encouraged if ANC < 500/mm^3

5.4.2. **Imaging Contrast (CT).** Imaging contrast for CT should not be administered on the same day with ascorbate infusion. If administered within the same day, monitor liver function tests and contact the medical monitor for the IND.

5.4.3. **Imaging Contrast (MRI).** Use of imaging contrast for MRI is permitted on the same day as ascorbate infusion.

5.4.4. **CYP450 3A4 interactions**. Review drugs for the potential for interactions. Medically monitor subjects receiving a potentially interactive drug.

5.4.5. **Warfarin (coumadin)**. Warfarin has a theorized interaction with high-dose ascorbate and must not be prescribed. Subjects requiring warfarin (coumadin) therapy should be removed from trial.

5.4.6. **Hyperuricemia** (gout)**.** Initial dose of colchicine should be 0.6 mg with a subsequent dose of 0.3 mg an hour later if the first dose is well-tolerated. Liver function tests (AST / ALT) should be monitored.

5.4.7. **Hypertension.** Subjects should have blood pressure monitored at the start of each cycle. For subjects with documented hypertension, treating physicians should consider subsequent monitoring. Hypertensive medication should be initiated or increased for optimal blood pressure control according to standard public health guidelines.

5.4.8. **Fluid intake.** Subjects will be encouraged to maintain adequate hydration to decrease the risk of nephrolithiasis. Those unable to maintain oral hydration should be considered for supplemental IV hydration per institutional care guidelines.

5.4.9. **G-CSF products**. The use of G-CSF products is allowed on the study per the treating physician's discretion.

5.4.10. **Palliative Radiotherapy**: Palliative radiotherapy, unless required due to progressive disease, is permitted during the study. Area receiving palliative radiation should be different than target lesion/s to utilized for RECIST response assessment. Patient will not receive concurrent protocol specified therapy until completion of radiation. Study therapy may resume (chemotherapy and ascorbate infusions) as per study protocol after 72 hours of completing radiation therapy or when acute toxicities related to radiation resolve to CTCAE grade 2 or less. Therapy is not delayed for hair loss and/or decreased lymphocyte count.

5.5. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 4 cycles or until criteria for removal is met (Section 5.7). If there are delays due to adverse events, continuation of the protocol and continued treatment will be determined by the treating medical oncologist and IND sponsor.

5.6. Duration of Follow Up

5.6.1. **Early termination.** Subjects who withdraw or were removed from study prior to completing all 4 cycles of therapy will be followed a minimum of 21 days from the final ascorbate infusion (Section 5.8.1). Further follow-up is per investigator discretion.

5.6.2. **Completed therapy.** Subjects who complete all four cycles of therapy will be followed passively for 2 years from the end of study-directed therapy. Follow-up assessments are listed in Section 6.5. Post study therapy follow-up appointment will be 28 d (± 1 calendar week) after the last infusion of study drug. Further follow-up will be per standard of care and subjects will be followed passively for events (progression of disease or death). .

5.7. Criteria for Removal from Treatment

5.7.1. **Progressive disease** (as defined by RECIST 1.1[33])

5.7.2. **Extraordinary medical circumstances.** If at any time the constraints of this protocol are detrimental to the patient's health, the patient will be removed from protocol therapy. In this event, the reasons for withdrawal will be documented.

5.7.3. **Patient's refusal** to continue treatment. In this event, the reasons for withdrawal will be documented.

5.8. End of Study Visit (early termination)

If a subject is removed from study, or elects to withdraw, an End-of-Study (EOS) visit should be scheduled within 7 calendar days of the decision. End-of-Study does not apply to subjects who complete all 4 cycles of chemotherapy.

5.8.1. **Minimum follow-up.** Every effort will be made to follow patients off study for toxicity for 28 days (±7 calendar days to accommodate scheduling) after removing the subject from study. If the subject is removed due to toxicity, follow-up should continue until ascorbate-associated adverse events are resolved.

5.8.2. **Labs.** CBC w/diff and a comprehensive metabolic panel should be ordered when the subject is removed from study (within 7 calendar days). If labs were ordered clinically within window, these can be used at the discretion of the medical monitor, sponsor, and investigator.

5.9. Additional Therapy

Subjects who have left study, or who have completed the chemotherapy treatment, may continue standard therapies or other clinical trials at the discretion of their treating medical and radiation oncologists. This treatment is beyond the scope of the protocol, as these patients have completed participation in the protocol.

6. ASSESSMENTS

After initial disease progression, subjects will receive salvage care as prescribed by their oncology team. Follow-up will be maintained through chart review and/or visits with clinical personnel. Subjects should have life-long follow-up for this study.

6.1. Pre-treatment Assessments (baselines)

Baseline assessments should be performed within 21 days of the start of therapy; they may be completed C1D1 pre-therapy.

6.1.1. Fatigue
6.1.2. Neuropathy
6.1.3. Infection
6.1.4. Nausea
6.1.5. Vomiting
6.1.6. Pain (headache)
6.1.7. Comprehensive metabolic panel (screening or cycle 1 d 1)
6.1.8. Complete blood count with differential (screening or cycle 1 d 1)
6.1.9. Uric acid (baseline only)
6.1.10. Ascorbate levels (draw this prior to the 15g test dose). Draw in a 4mL green-top Na Heparin tube.
6.1.11. Finger-stick glucose. The finger-stick glucose should be done at the same time as the ascorbate level blood draw. **This is research only** and should not be entered into the medical record, only recorded in the study chart.
6.1.12. Blood sample for ROS testing (draw prior to the 15g test dose). Draw 5-6 cc in a pink-top tube and put on ice for transport.
6.1.13. Iron panel (Iron, transferrin, TIBC, and % saturation)
6.1.14. Ferritin

6.2. Assessments During Chemotherapy

Assessments will be done once at the start of each chemotherapeutic cycle. No further assessments are required during the treatment cycle.

6.2.1. Fatigue
6.2.2. Neuropathy
6.2.3. Infection
6.2.4. Nausea
6.2.5. Vomiting

6.2.6. Pain (headache)

6.2.7. Comprehensive metabolic panel (screening may be used for cycle 1 d 1 per physician discretion) (may be done up to 1 week before cycle day 1)

6.2.8. Complete blood count with differential (screening may be used for cycle 1 d 1 per physician discretion) (may be done up to 1 week before cycle day 1)

On cycle day 1 (D1):

6.2.9. Ascorbate levels – prior to infusion. Draw in a 4mL green-top Na Heparin tube.

6.2.10. Blood sample for ROS testing – prior to infusion. Draw in a 5-6 cc pink top (EDTA) tube and put on ice for transport.

6.2.11. Ascorbate levels – end of ascorbate infusion. Draw in a 4mL green-top Na Heparin tube.

6.2.12. Finger-stick glucose using research glucometer. Test prior to ascorbate infusion and at the end of infusion (i.e., at the same time as the blood draws for ascorbate levels). This is research only and should not be entered into the medical record, only recorded in the study chart. The finger-stick glucose should be done at the same time as the post-infusion ascorbate level blood draw. The research glucometer will give an elevated reading that does not represent blood glucose, but blood ascorbate (serum/plasma glucose *via* pathology tests remains unaffected) (Ma and Drisko, 2013). Subjects should be informed fingerstick glucose is inappropriate for them and that healthcare providers will need to check blood glucose through a blood draw.

On cycle day 2 (D2):

6.2.13. Blood sample for ROS testing – pre-infusion. Draw in a 5-6 cc pink top (EDTA) tube and put on ice for transport.

6.2.14. **Cycles 1 and 3 only**. Order an iron panel (Iron, transferrin, TIBC, and % saturation) and ferritin. Results should be entered into the medical record.

6.3. Assessments During Ascorbic Acid Infusions

Blood pressure should be done, at minimum, pre- and post-infusion for each infusion. If the infusion runs for longer than 1 hour, blood pressure assessment should be done in the interm as clinically indicated.

Pre-infusion is defined as any time during the same calendar day prior to infusion.

Post infusion is ≤ 15 minutes from end of infusion.

6.4. Radiologic Assessments (CT imaging)

CT imaging of the chest/abdomen/pelvis should be obtained for the following time-points and should be consistent with standard-of-care imaging done at the UIHC. **CT imaging with contrast cannot be performed on the same day as an ascorbate infusion.**

6.4.1. Baseline (≤ 30d of cycle 1, day 1)

6.4.2. End of cycle 2 (± 7 days of cycle 2, day 21)

6.4.3. End of cycle 4 (± 7 days of cycle 4, day 21)

6.5. Follow-up Assessments

The following assessments should be done at follow-up visits after completion of protocol-directed therapy. The Post-study therapy follow up is 28 days after the last ascorbate infusion (± 1 calendar week to coincide with other clinical appointments).

6.5.1. (Post study therapy follow-up) Blood sample for ROS testing. Draw 5-6 cc in a pink-top tube and put on ice for transport [this sample should be drawn regardless of additional therapy; can be drawn subsequent cycles D1 if within window].

6.5.2. (Post study therapy follow-up) CBC w/differential

6.5.3. (Post study therapy follow-up) Comprehensive metabolic panel.

6.5.4. If labs were ordered for another clinic visit, and within window, these can be used at the discretion of the medical monitor, sponsor, and investigator.

6.5.5. Further follow up is per standard of care. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months for 2 years. Lab information, including CBC w/differential and plasma chemistries, ordered for standard of care or other reasons may be pulled from subsequent follow-up visits or physician's visits, for the purposes of monitoring treatment effects and adverse events long-term.

6.5.6. Medical record information will be reviewed for the purposes of monitoring treatment effects and adverse events long-term.

6.5.7. Follow up CT scans as clinically indicated for standard of care

6.6. End of Study Assessments

The following assessments should be performed when a criteria for removal is met (Section 5.7). An End-of-Study (EOS) visit should be scheduled within 7 calendar days of the decision. An existing clinical visit may be used for the EOS visit.

6.6.1. **Minimum follow-up.** Every effort will be made to follow patients off study for toxicity for 21 days after removing the subject from study. If the subject does not return to clinic, phone call contact is acceptable. If phone call contact cannot be made, and the subject does not return a phone call, documentation should be made of at least 3 attempts.

6.6.2. **Adverse event follow-up**. The participant will be followed clinically or the local provider contacted (as appropriate) until all ascorbate-associated adverse events have resolved/stable.

6.6.3. **Labs.** CBC w/diff and a comprehensive metabolic panel should be ordered when the subject is removed from study (+ 7 calendar days). If labs were ordered clinically within window, these can be used at the discretion of the medical monitor, sponsor, and investigator.

7. DRUG THERAPY

7.1. Carboplatin. Please refer to the FDA approved package insert for additional information.

7.1.1. **Availability**. Commercially available for multiple strengths as a generic drug.

7.1.2. **Compatibility**. Compatible with D5W (dextrose 5%) and NS (Normal saline – sodium chloride 0.9%).

7.1.3. **Storage and stability**. Unopened vials of carboplatin aqueous solution for injection are stable to the date indicated on the package when stored at 25°C (77°F); excursions permitted from 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light. Carboplatin aqueous solution multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries. Parenteral drug products should be inspected visually for particulate matter

and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

7.1.4. **Black box warning**. Bone marrow suppression with carboplatin is dose-related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect. Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration

7.1.5. **Toxicities**. The most common adverse reactions include alopecia, hypocalcemia, hypokalemia, hypomagnesia, hyponatremia, abdominal pain, diarrhea, nausea, vomiting, anemia, leukopenia, neutropenia, thrombocytopenia, elevated alkaline phosphatase, elevated AST/SGOT, abnormal blood urea, elevated serum creatinine, and pain. Serious adverse events include myelosuppression, hypersensitivity reaction (~ 2%), and unexplained visual loss/visual disturbance.

7.2. Paclitaxel. Please refer to the FDA approved package insert for additional information.

7.2.1. **Availability**. Commercially available for multiple strengths as a generic drug.

7.2.2. **Compatibility**. Compatible with D5W (dextrose 5%) and NS (Normal saline – sodium chloride 0.9%).

7.2.3. **Storage and stability**. Unopened vials of paclitaxel for injection are stable until the date indicated on the package when stored between 20°–25°C (68°–77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25°C) and lighting conditions for up to 27 hours. Store the vials in original cartons between 20°–25°C (68°–77°F). Retain in the original package to protect from light.

7.2.4. **Black box warning**. Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving Paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Patients who experience severe hypersensitivity reactions to Paclitaxel should not be rechallenged with the drug. Paclitaxel therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Paclitaxel.

7.2.5. **Toxicities**. The most common adverse reactions (≥10%) flushing, abnormal ECG, edema, hypotension, alopecia, rash, nausea, vomiting, diarrhea, mucositis, stomatitis, abdominal pain, neutropenia, leukopenia, anemia, thrombocytopenia, elevated

alkaline phosphatase, elevated AST, injection site reaction, peripheral neuropathy, arthralgia/myalgia, weakness, increased creatinine, infection. **Serious adverse events include hypersensitivity reaction.**

7.3. Ascorbic Acid Injection, USP; Ascorbate; NDC 67457-118-50

7.3.1. **Availability**. IND 105715 utilizes two available drug product from McGuff Pharmaceuticals, Inc. and Bioniche Pharma USA LLC. McGuff Pharmaceuticals, Inc. is the preferred supplier.

7.3.2. **Ascor L-500 (ascorbic acid injection, USP) (McGuff Pharmaceuticals, INC)** is available under IND authorization only (IND 105715) for trials contracted to McGuff from the sponsor. Drug is available in sterile 50 mL vials containing 25 g of ascorbic acid (500 mg/mL)

7.3.3. **Ascorbic Acid Injection, USP (Bioniche Pharma USA LLC)** is a commercially available injection available in sterile single-use 50 mL vials containing 25 g of ascorbic acid (500 mg/mL).

7.3.4. **Compatibility**. Ascorbate is considered a CYP4503A4 inducer.[32] Therefore close monitoring of subjects who may be concomitantly receiving CYP3A4 substrates with narrow therapeutic indexes for toxicities is required. A table of CYP3A4 substrates, inhibitors, and inducers is provided in the Appendix. Ascorbate may decrease plasma/blood concentrations of **substrates** (Appendix B, tables 1, 2, and 3). Ascorbate may increase CYP3A4 induction (Appendix B, Table 4). CT imaging contrast should not be given on the same day as an ascorbate infusion.

7.3.5. **Storage and Stability**. Unopened vials of Ascorbic Acid for Injection USP are stable until the expiration date indicated on the package when stored between 2° – 8°C (36°–46°F). Protect from light and store in the carton until time of use.

7.3.6. **Toxicities**. Diarrhea, nausea and/or vomiting, kidney stones, dry mouth/thirst, headache, abdominal pain, fatigue, facial flushing, sweating, weakness, injection site irritation, and faint/dizzy (after rapid infusion) have been reported in the literature. When administered on the same day as CT imaging contrast, liver function tests may be elevated. Recommendation is to not schedule CT imaging with contrast on the same day as an ascorbate infusion.

8. DOSE MODIFICATIONS AND DELAYS

8.1. Hypersensitivity reactions—Paclitaxel

8.1.1. **Non-Life threatening**. Stop paclitaxel infusion and consider / per physician discretion

- Methylprednisone sodium succ 125 mg intravenously
- Benadryl 25-50 mg IV
- Famotidine 20 mg IV

Twenty minutes after resolution of the reaction symptoms, resume paclitaxel infusion at a slower rate per the chemotherapy suite protocol at UIHC. If the subject reacts again to paclitaxel in the same day, then remove from the study

8.1.2. **Life threatening reaction**. Stop paclitaxel and proceed with anaphylaxis management as indicated – treatment suggestions per below:

- Keep infusion-related anaphylaxis kit available. Call physician immediately for severe reactions.
- EPINEPHrine 0.3 mg, intramuscular, once as needed.

- Methylprednisolone sodium succ 125 mg, intravenous, once as needed.
- Benadryl 50 mg, intravenous, once as needed.
- BLS/ACLS intervention as needed.

Subject will be removed from the study. Reaction must be filed as a life-threatening adverse event (expected).

8.2. Hematologic toxicities—paclitaxel and carboplatin

8.2.1. **Febrile neutropenia**. Febrile neutropenia is defined as temp of 38.2 C (100.8F) and ANC < 500. In addition to management of febrile neutropenia per standard of care that includes antibiotics and infectious work up as needed, the interventions below will be conducted for subsequent treatment cycles without reverting to the previous chemotherapy dose

Neutropenic Fever	Carboplatin (AUC)	Paclitaxel (mg/m^2)	G-CSF
None	6	200	None
1st episode	6	200	Yes
2nd episode	5	160	Yes
3rd episode	4	130	Yes

8.2.2. **Neutropenia and thrombocytopenia** (on the date of chemotherapy: management and chemotherapy dose adjustment). Carboplatin and paclitaxel will be dose reduced per the guidelines below. Once the dose has been reduced, this will apply to the subsequent cycles.

ANC		Platelets	Carboplatin (AUC)	Paclitaxel (mg/m^2)
≥ 1,500	and	100,000	6	200
1,000 – 1,499	or	75,000 – 99,999	4	140
< 1,000	or	< 75,000	Delay*	Delay*
< 500[§]			Delay*	Delay*

* Check CBC w/diff weekly and resume treatment when ANC ≥1,000 and platelets ≥ 75,000. The treatment can be delayed for a maximum of 3 weeks.

[§] consider prophylactic ciprofloxacin 500 mg orally twice daily as long as ANC is <500

8.3. Non-Hematologic Toxicity—paclitaxel and carboplatin

8.3.1. **Gastrointestinal**. Nausea and vomiting treatment per the treating physician's discretion. Use Zofran (ondansetron) with caution as this medication may be less efficacious with high-dose ascorbic acid.

8.3.2. **Neurotoxicity**. Chemotherapy dose modification as shown below

Neurotoxicity	Carboplatin (AUC)	Paclitaxel (mg/m^2)
Grade 1	6	200
Grade 2	5	175
Grade 3	Delay*	Delay*

* evaluate weekly and resume chemotherapy when neurotoxicity < grade 3. The treatment can be delayed for a maximum of 3 weeks.

8.3.3. **Fatigue**. This can be a side effect from chemotherapy. Consider treating with dexamethasone 4 mg orally twice daily for 3 days following the day of chemotherapy. Otherwise, chemotherapy dose adjustment as shown in the table below. Once chemotherapy reduced, there will be no dose re-escalation in the subsequent cycles.

Fatigue	Carboplatin (AUC)	Paclitaxel (mg/m^2)
Grade 1	6	200
Grade 2	5	175
Grade 3	Delay*	Delay*

* evaluate weekly and resume chemotherapy when fatigue < grade 3. The treatment can be delayed for a maximum of 3 weeks.

8.3.4. **Hepatotoxicity**. Adjust paclitaxel as shown below. No dose adjustment needed for carboplatin. Rule out other causes for hepatotoxicity.

AST or ALT		Bilirubin mg/dl	Paclitaxel (mg/m^2)
<2.5 x ULN	and	<1.5	200
2.5 - 5.0 x ULN	and	<1.5	100
>5.0 x ULN	or	>1.5	Delay*

* evaluate weekly and resume chemotherapy when AST and ALT are both at < 5.0xULN and bilirubin is < 1.5 mg/dL. Treatment can be delayed for a maximum of 3 weeks.

8.3.5. **High body mass index** (carboplatin). This will only affect the dose of carboplatin, not paclitaxel. The maximum allowed calculated creatinine clearance will be 125 mL/min (males) and 125 mL/min (females).

8.4. Ascorbate

8.4.1. **Dose modifications**. There are no dose adjustments for toxicities.

8.4.2. **Dose delays**. Doses may be delayed by up to three weeks with treating physician and PI approval. Reason for treatment delay should be noted in the study chart. Missed doses should not be made up.

8.4.3. **Test/retest**. If an unexpected adverse event is observed, the treating physicians may withhold ascorbic acid for up to 1 calendar weeks to determine if the effect diminishes or resolves entirely. Considering the nature and severity of the event, if reasonable ascorbic acid should then be continued to determine if the event again presents. This will function as a test for causality.

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will also be monitored by internal oversight specialists at the University of Iowa. *The Data and Safety Monitoring Plan of the Holden Comprehensive Cancer Center* provides standard operating procedures to monitor all clinical cancer trials at the UIHC. All investigator-initiated trials are automatically monitored by the Data and Safety Monitoring Committee (DSMC). A detailed data and safety monitoring plan for this study is provided (Appendix). This study has been assigned as a **risk level 4** as a physician sponsored IND phase study.

9.1. Determination of Reporting Requirements

An adverse event (AE) is defined in the *CTEP, NCI Guidelines* [2005] as "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure (attribution of unrelated, unlikely, possible, probably or definite)."

9.1.1. **Adverse event recording.** The clinical research team is responsible for identifying, collecting, and recording clinical data, including adverse events, through 21 days after the last dose of study drug (ascorbate).

9.1.2. **Adverse event grading.** Adverse events will be graded according to NCI's Common Toxicity Criteria (CTCAE v4). Grading may be done by any licensed medical personnel (e.g., research nurse, treating physician, etc.) with final determination made by the principal investigator.

9.1.3. **Adverse event attribution**. Initial attribution of ascorbate to a grade 3 or greater event may be assigned by any licensed medical personnel (e.g., research nurse, treating physician, etc.). The principal investigator will make the final determination regarding the attribution of the study drug to the adverse event and also decide course of action for the study participant. CTCAE grade 2 and lesser events do not require attribution *unless* the event is unexpected (i.e., not related to chemotherapy, tumor, or previously diagnosed underlying condition).

9.2. Routine Adverse Event Reporting Requirements

Adverse events attributed to the study drug will be reported to the Data Safety Monitoring Committee (DSMC) *via* the Clinical Research Safety Officer (CRSO) following established standard operating procedure of the DSMC.

9.3. Expedited Adverse Event Reporting

Investigators MUST immediately report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). Reporting requirements are in Table 2.

An adverse event is considered serious if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Table 2: CTEP/NCI's Recommended Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention (Phase 1 and Early Phase 2 Studies)[1]

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Adverse events that are not deemed serious are reported through routine adverse event requirements.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

Effective Date: May 5, 2011

10. CORRELATIVE/SPECIAL STUDIES

10.1. Parameters of Oxidative Stress.

Research blood for ROS testing will be obtained at each cycle:

- Cycle day 1, prior to ascorbate infusion
- Cycle day 2, prior to infusion

In addition, the last ROS blood sample will be obtained at the first follow-up visit (protocol section 6.5 Follow-up Assessments) prior to any therapy that would be administered that day.

ROS research samples are 5-6 mL in an EDTA tube (pink top) and placed immediately on ice. The basic science RA must be contacted immediately after the blood draw is obtained. Samples should be spun to yield plasma using standard procedures as soon as possible. Plasma should then be transferred to a cryovial and frozen immediately at -80°C. It is imperative that plasma is not thawed until analysis in the Eicosanoid Core Laboratory as F_2-IsoPs can be generated in plasma *ex vivo*, even at temperatures of -20°C. A minimum of 1 mL plasma is required for analysis. This research analysis will not be added to the subject's medical record.

10.2. Patient Reported Outcomes (optional)

Previous studies demonstrated the potential for increase in toxicities when multiple anti-cancer agents were combined to treat patients with non-small cell lung cancer. The FACT questionnaires (the FACT-Lung (FACT-L) and FACT-Taxane (FACT-Tax)) will be used in this study to capture the subject's assessment of their overall quality of life (QOL), disease symptoms and treatment related side effects. Both of these instruments have been rigorously validated.[34,35]

Results of FACT-L will be reported as:

- Trial Outcome Index-Lung (TOI-L): Sum of FACT-L subscales (PWB + FWB + LCS)
- Total FACT-L: Sum of all FACT-L subscales (PWB + SWB + EWB + FWB + LCS)
- LCS subscale

Where the higher score indicates a better quality of life.

Results of FACT-Tax will be reported as:

- Taxane subscale
- Neurotoxicity Subscale

Where a higher the score indicates higher treatment related toxicities.

10.2.1. Questionnaires administration timings

FACT-L and FACT-Tax questionnaire are administered:

- Baseline (before receiving any trial therapy; can be on C1D1)
- Day 1 of each subsequent cycle of chemotherapy (i.e., C2, C3, C4)
- On the day of last ascorbate infusion (approximately 12th week of the trial)

10.2.2. Analysis

The objective of the PRO assessment in this study is to describe changes in subject reported QOL, lung cancer symptoms, and treatment related-toxicities by using FACT-L/Taxane questionnaires. Changes in LCS, FACT-L, TOI-L, Taxane and Neurotoxicity subscale scores will be calculated from baseline to week 12 and summarized with means. Additionally, proportions of patients experiencing clinically meaningful changes will be calculated. Clinically meaningful changes in each of the subscale of these questionnaires, TOI-L, and Total FACT-L have been pre-defined and validated in the previous studies and are defined in the table below.

Established threshold values corroborating with clinically meaningful change for each subscale or indices of the FACT- L & FACT-Tax instrument:

Instrument	Scale/Subscale	Clinically meaningful change (points)	Reference
FACT-L	LCS	3	Cella *et al* 2002[36]
	Total FACT-L	9	
	TOI-L	6	
FACT-Taxane	Taxane-Subscale	3	Cella *et al* 2003[34]
	Neurotoxicity Subscale	3	

Based on the differences in subscale scores over time, study subjects will be categorized to have improved, remained stable or worsened in terms of their quality of life and have either developed significant or no-significant treatment related neurotoxicity.

- **Improved health-related QOL**: if the magnitude of increase in LCS, TOI-L and FACT-L score from baseline to week 12 is equal or greater than the established threshold for these scales/subscale.
- **Worsened health-related QOL**: if the magnitude of decrease in his or her LCS, TOI-L and FACT-L score from baseline to week 12 is equal or greater than the established threshold.
- **Stable health-related QOL**: if the change does not fall into any of the above category.
- **Significant paclitaxel related neurotoxicity**: if the magnitude of increase in the taxane and/or neurotoxicity subscale score from baseline to week 12 is equal or greater than established threshold.
- **Non- significant paclitaxel-related neurotoxicity:** if the magnitude of increase in the taxane and neurotoxicity score from baseline to week 12 is less than previously established threshold for these scales.

Mean changes and category-specific proportions will both be reported along with 95% confidence intervals, and compared descriptively to previously published studies.[37,38]

11. STUDY CALENDAR

	screen[a]	therapy	end of study[b]	F/U[c]
History[d] & physical[d]	X	d1	X	X
Vitals (BP, temp, HR)[e]	X	*e*	X	
Weight, BSA[f]		*f*	X	
G6PD[a]	X			
Uric Acid		baseline		
Iron panel, ferritin		*s*		
Pregnancy test[a]	X			
Ascorbate 15g test dose	X			
HRQOL (optional)		X[r]		
Comprehensive metabolic panel[g]	X[a]	d1[g]	X	X[c]
CBC w/diff	X[a]	d1	X	X[c]
Ascorbate infusion[h,e]		X[h,e]		
Blood for ascorbate levels[i]	X	X[i]	X	
Blood for ROS[k]	X	X[k]	X	X
Adverse events[m]	X[m]	X	X	X
CT, chest/abdomen/pelvis[n]	X	X[n]		
Brain MRI[o]		X[o]	X[o]	X[o]
PET or bone scan[o]		X[o]	X[o]	X[o]
Survival[p]				X[p]

a study day 1 is cycle 1, day 1. Screening labs and history/physical must be obtained ≤ 21d from d1. G6PD may be obtained at any time prior to test dose as the value does not fluctuate. Pregnancy test at physician discretion.

b off-study evaluation (if subject is removed from study or withdraws), ± 7 calendar days from removal. Follow at least monthly until resolution of all ascorbate-associated adverse events or a new baseline is established. There should be a follow-up visit 28d (± 7d) after the last ascorbate infusion (preferably in person, phone call is acceptable); Section 5.8

c Follow-up is 28d (±1 calendar week) after the last ascorbate infusion; further follow-up is passive through chart review. Obtain lab & research assessments at 28d follow-up only. See 5.6.2.

d history is only taken at the screening and/or baseline visit; screening physical should be done within 21d of C1D1 and then on D1 of each cycle (physical can be up to/including –1 week)

e blood pressure should be obtained before and after (≤ 15 min EOI) ascorbate infusion

f chemotherapy calculations using actual body weight, see section 5.3.3 and 5.3.4

g comprehensive metabolic panel: albumin, total bilirubin, calcium, CO2, creatinine, glucose, alkaline phosphatase, potassium, total protein, sodium, ALT, AST, BUN, chloride; labs for D1 of chemo can be up to/including –1 week.

h twice weekly through 4 cycles of paclitaxel/carboplatin. See sections 6.2, 6.3, and 6.4 for assessments

i Draw blood specimens ~4cc green top tube pre- and post- infusion drawn once per cycle.
At the same time, use a finger-stick glucometer (study provided) to obtain ascorbate levels.
Do not chart in medical record; store only in research record.

k Draw 1 EDTA pink-top tube (5-6 mL) D1 pre-infusion and D2 pre-infusion. Also draw 1 sample at FU#1 prior to any subsequent therapy..

m baseline constitutional assessment should be done at screening and/or prior to infusion on cycle 1, day 1.

n baseline obtained ≤ 30d from d1; obtain after cycle 2 and after cycle 4 (approximately 21 – 28 days after d1)
DO NOT schedule on days with ascorbate infusions. Ascorbate and CT contrast are contraindicated.

o at the discretion of the treating physician

p through passive chart review

r baseline (before therapy D1), then D1 of each subsequent cycle, then prior to last ascorbate infusion.

s draw at baseline and only on day 2 of cycles 1 and 3

12. MEASUREMENT OF EFECT

12.1. Tumor Response (Primary End-Point)

Tumor response will be defined using the RECIST 1.1 guidelines.[33]

12.2. Progression Free Survival

Time from start of therapy (day 1, cycle 1) to documented disease progression. Progression will be defined using the RECIST 1.1 guidelines.[33]

12.3. Overall Survival

Time from start of therapy (day 1, cycle 1) to death.

12.4. Toxicity

Categorize and quantify adverse events from start of therapy (day 1, cycle 1) to end of cycle 4.

13. STATISTICAL CONSIDERATIONS

13.1. Endpoints

- Tumor response
- Time to progression
- Progression free survival (PFS)
- Overall survival (OS)

13.2. Analysis Plan

The primary objective of this trial is to evaluate initial tumor response. A response rate above 40% is considered clinically important, whereas a rate below 20% is considered uninteresting. In statistical terms, we are testing the null hypothesis H0: $\pi < 0.20$ versus the alternative H1: $\pi > 0.40$, where π is the probability of response. Sample size requirements for the trial are based on an optimal Simon two-stage design. Seventeen (17) patients will be enrolled in the first stage, and the study terminated if 3 or fewer respond. Otherwise, an additional 20 patients will be enrolled in the second stage. If 11 or more of the 37 total patients respond, the treatment will be deemed worthy of further study. The proposed design has an average sample size of 26.0 and a probability of early termination equal to 0.55. Furthermore, the design will ensure a 0.90 probability of correctly identifying an effective treatment. Conversely, if the treatment is not effective, there is a 0.10 probability of incorrectly concluding that it is. For the secondary objectives, time to progression, progression-free survival, and overall survival will be estimated with the methods of Kaplan-Meier. Estimated survival probabilities will be plotted and medians reported, along with 95% confidence intervals.

13.3. Accrual Strategy

The Holden Comprehensive Cancer Center consults approximately 300 new lung cancer patients per year. Of these, approximately 60% are staged IIIB or greater. This results in approximately 160 potential participants with an expected accrual rate of 12% and enrollment rate of 10%. This results in an estimated enrollment of 16 subjects per year, closing the trial to accrual in approximately 2 ½ years.

13.4. Study Duration

The study is expected to close to accrual in 2.5 years with primary objective being completed by year 3. With a median survival of 9 months, the study's duration to complete the secondary objectives should be 4 years.

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PROTOCOL APPENDIX A : 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 not 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.

PROTOCOL APPENDIX B: CYP3A4 INTERACTION TABLE

CYP3A4 INTERACTION TABLE (Ascorbate may decrease the plasma/blood concentrations of substrates) Drugs with ~~strikeout~~ text are antiretroviral drugs that are not allowed for use on this study. * 3A4 substrate & inhibitor; # 3A4 substrate & inducer			
abiraterone	acetaminophen	ado-trastuzumab	alfentanil
alfuzosin	aliskiren	alitretinoin	almotriptan
alprazolam	ambrisentan	amiodarone*	amitriptyline
amlodipine	amprenavir	apixaban	aprepitant*
aripiprazole	armodafinil#	artemether	asenapine
astemizole	atazanavir*	atorvastatin	avanafil
axitinib	beclomethasone	bedaquiline	benzphetamine
bexarotene	bisoprolol	boceprevir	bortezomib
bosentan#	bosutinib	brentuximab	bromazepam
bromocriptine	budesonide	buprenorphine	buspirone
busulfan	cabazitaxel	cabozantinib	caffeine
canagliflozin	carbamazepine#	cevimeline	chlordiazepoxide
chloroquine	chlorpheniramine	ciclesonide	cilostazol
cinacalcet	cisapride	citalopram	clarithromycin*
clindamycin	clobazam	clomipramine	clonazepam
clopidogrel	clorazepate	clozapine	cobicistat*
cocaine	codeine	colchicine	conivaptan*
crizotinib	cyclobenzaprine	cyclophosphamide	cyclosporine*
dantrolene	dapsone	darifenacin	~~darunavir~~
dasatinib	delavirdine*	desogestrel	dantrolene
dexamethasone#	dexlansoprazole	dextromethorphan	diazepam
diclofenac	dienogest	dihydroergotamine	diltiazem*
disopyramide	docetaxel	dofetilide	dolasetron
domperidone	donepezil	doxorubicin	dronedarone
droperidol	dutasteride	efavirenz*#	eletriptan
elvitegravir	enzalutamide	eplerenone	ergoloids
ergonovine	ergotamine	erlotinib	erythromycin*
escitalopram	esomeprazole	estazolam	estradiol
estradiol valerate	estrogens	eszopiclone	ethinyl estradiol
ethosuximide	etonogestrel	etoposide	etravirine
everolimus	exemestane	felbamate	felodipine

CYP3A4 INTERACTION TABLE (Ascorbate may decrease the plasma/blood concentrations of substrates) Drugs with ~~strikeout~~ text are antiretroviral drugs that are not allowed for use on this study. * 3A4 substrate & inhibitor; # 3A4 substrate & inducer			
fentanyl	fesoterodine	fexofenadine	finasteride
fingolimod	flunisolide	flurazepam	flutamide
fluticasone	~~fosamprenavir~~*	fosaprepitant	fulvestrant
galantamine	gefitinib	granisetron	guanfacine
haloperidol*	hydrocodone	hydrocortisone	ifosfamide
iloperidone	imatinib*	imipramine	indacaterol
~~indinavir~~*	irinotecan	isosorbide dinitrate	isosorbide mononitrate
isradipine	itraconazole*	ivacaftor	ixabepilone
ketamine	ketoconazole*	lansoprazole	lapatinib
lercanidipine	letrozole	levonorgestrel	lidocaine*
linagliptin	lomitapide	loperamide	~~lopinavir~~
loratadine	losartan	lovastatin	lumefantrine
lurasidone	~~maraviroc~~	marijuana	medroxyprogesterone
mefloquine	meloxicam	mestranol	methadone
methylergonovine	methylprednisolone	miconazole*	midazolam
mifepristone	mirabegron	mirtazapine	modafinil
mometasone	montelukast	nateglinide	nefazodone*
~~nelfinavir~~*	~~nevirapine~~#	nicardipine*	nifedipine
nilotinib	nimodipine	nisoldipine	nitrendipine
norethindrone	norgestrel	nortriptyline	omeprazole
ondansetron	ospemifene	oxybutynin	oxycodone
paclitaxel	paliperidone	palonosetron	pantoprazole
paricalcitol	paroxetine	pazopanib	perampanel
perphenazine	pimozide	pioglitazone	pomalidomide
ponatinib	prasugrel	prednisolone	prednisone
primaquine	progesterone/ progestins	propafenone	propranolol
quazepam	quetiapine	quinidine*	quinine
rabeprazole	ramelteon	ranolazine	regorafenib
repaglinide	rifabutin#	~~rilpivirine~~	risperidone
~~ritonavir~~*	rivaroxaban	roflumilast	romidepsin
ruxolitinib	salmeterol	~~saquinavir~~*	saxagliptin

CYP3A4 INTERACTION TABLE (Ascorbate may decrease the plasma/blood concentrations of substrates) Drugs with ~~strikeout~~ text are antiretroviral drugs that are not allowed for use on this study. * 3A4 substrate & inhibitor; # 3A4 substrate & inducer			
selegiline	sertraline	sibutramine	sildenafil
silodosin	simvastatin	sirolimus	sitagliptin
solifenacin	sorafenib	sufentanil	sunitinib
tacrolimus	tadalafil	tamoxifen	tamsulosin
~~telaprevir~~	telithromycin*	temsirolimus	teniposide
terfenadine	testosterone	tetracycline*	theophylline
tiagabine	ticagrelor	ticlopidine	tinidazole
~~tipranavir~~	tofacitinib	tolterodine	tolvaptan
topotecan	toremifene	tramadol	trazodone
triazolam	trimethoprim	trimetrexate	trimipramine
ulipristal	vandetanib	vardenafil	vemurafenib
venlafaxine	verapamil*	vilazodone	vinblastine
vincristine	vinorelbine	vismodegib	voriconazole
warfarin	zaleplon	zileuton	ziprasidone
zolpidem	zonisamide	zopiclone	

References:

1. Lexi-comp On-line. Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. (accessed 1/16/15)
2. Pharmacist's Letter/Prescriber's Letter. Cytochrome P450 Drug Interactions. October 2013.
3. P450 Drug Interaction Table. Indiana University Department of Medicine Division of Clinical Pharmacology. http://medicine.iupui.edu/clinpharm/ddis/main-table/
4. Hansten and Horn's Drug Interactions Analysis and Management. Facts and Comparisons. 2014

UIHC Drug Information Center: 1/15

PROTOCOL APPENDIX C: DATA AND SAFETY MONITORING PLAN

In accordance with the NIH policy on procedures for data and safety monitoring of clinical trials, the Holden Comprehensive Cancer Center (HCCC) has developed systems to ensure the safety of participants, the validity and integrity of research data, and compliance with the approved protocol. HCCC Principal Investigators are required to include a general description of a data and safety monitoring plan as part of each new interventional research protocol, which they develop and submit for review.

All investigator-initiated protocols will contain an appropriately detailed Data and Safety Monitoring Plan (DSMP) that will be reviewed and approved by the DSMC or Committee Chair. The DSMC dictates what constitutes a satisfactory plan for each study. All interventional clinical trials require monitoring for data veracity and safety, including physiologic, toxicity- and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III). The method and degree of monitoring needed is related to the degree of risk and should also be commensurate with size and complexity of the trial. The Clinical Research Safety Officer (CRSO) of the DSMC will be the primary interface with the study's PI and research team to collect and assemble all required materials for review by the Committee.

Risk Level

This protocol has been assessed by the Data and Safety Monitoring Committee (DSMC) of the HCCC and by the sponsor-investigator as a **Risk Level 4**. Specifically, a risk-level 4 clinical trial is one that has:

- A risk of death (i.e., 100-day treatment-related mortality) of >5%, or,
- A risk of a Grade 4 SAE (serious adverse event > 15%, or,
- An investigator-sponsored investigational new drug (IND), or,
- Gene therapy, gene manipulation, or viral vector systems, or,
- High-risk clinical procedures performed solely for research purposes, or
- A new chemical or drug for which there is limited or no available safety data in humans

Required DSMP elements

The Principal Investigator for institutional studies at the HCCC must include a trial-specific DSMP with each new protocol. The key items the plan must address are

- A subject eligibility check-list (inclusion / exclusion criteria)
- A list of expected toxicities
- Stopping rules for suspension of accrual secondary to adverse events and safety parameters
- PI's estimate of the study's risk level

The Principal Investigator is to ensure that all required data for monitoring is provided to the DSMC by way of the CRSO and the HCCC Protocol Manager.

Eligibility Checklist

Subject ID: _____ Date: _____

Inclusion criteria. All responses must be marked YES or NA for patient to be eligible

1. Histologically or cytologically confirmed NSCLC — Yes No
2. Cancer staged IIIB, IV, or recurrent (3.1.2) — Yes No
3. If CNS metastasis, metastasis is treated, no clinical signs of progression following treatment, and patient off steroids ≥ 3d (steroids must be prescribed specifically for brain metastasis) — Yes No
4. Tested G6PD status ≥ LLN — Yes No
5. Aged ≥ 18 years — Yes No
6. ECOG performance status of 0, 1, or 2 [KPS > 50] — Yes No
7. Screening labs within 21 days prior to cycle 1 day 1 — Yes No
    a. ANC ≥ 1500 cells/mm^3 — Yes No
    b. Platelets ≥ 100,000/mm^3 — Yes No
    c. Hemoglobin ≥ 8 g/dL — Yes No
    d. CRT ≤ 1.5 x ULN — Yes No
    e. TBIL ≤ 1.5 x ULN — Yes No
    f. ALT ≤ 3 times the UIHC upper limit of normal — Yes No
    g. AST ≤ 3 times the UIHC upper limit of normal — Yes No
8. Not pregnant — Yes No NA
   If N/A, state reason:_____
9. Agrees to adequate contraception during trial: — Yes No NA
   If N/A, state reason:_____
10. Tolerate one test dose (15g) of ascorbate — Yes No
11. Ability to understand & willingness to sign a consent document — Yes No

Signature: _____ Date: _____

Amendment 7 release (07 November 2018)

Eligibility Checklist

Subject ID: _____ Date: _____

Exclusion Criteria. All responses must be marked NO or NA for patient to be eligible

1.	Known sensitizing EGFR mutations or ALK gene rearrangement unless progression after targeted therapy. (If patient's biopsy did not allow EGFR or ALK gene analysis (e.g., inconclusive, not enough tissue, etc.), the patient is considered eligible for study.)	Yes	No	N/A
2.	PD-L1 expression of 50% or more on tumor cells (if available)	Yes	No	N/A
3.	Receiving warfarin therapy and cannot tolerate drug substitution	Yes	No	
4.	Known hemoptysis (more than ½ teaspoon per day) ≤ 1 week screen	Yes	No	
5.	Actively receiving insulin Exception is granted by IND sponsor, medical monitor, and PI.	Yes Yes	No	*or*
6.	Leptomeningeal disease	Yes	No	
7.	Receiving the following drugs and cannot be substituted			
	a. Flecainide	Yes	No	
	b. Methadone	Yes	No	
	c. Amphetamines	Yes	No	
	d. Quinidine	Yes	No	
	e. Chlorpropamide	Yes	No	
8.	Known active invasive malignancy	Yes	No	
9.	Other investigational agents with intent to treat	Yes	No	
10.	Uncontrolled intercurrent illness including, but not limited to:	Yes	No	
	a. Ongoing or active infection			
	b. Symptomatic congestive heart failure			
	c. Unstable angina pectoris			
	d. Cardiac arrhythmia			
	e. Psychiatric illness / social situations that would limit compliance			
	f. Other condition that would limit compliance with study requirements			
11.	Lactating woman	Yes	No	
12.	Known HIV-positive status	Yes	No	

Signature: _____ Date: _____

Expected toxicities

In addition to the standard toxicities of chemotherapeutic treatment for non-small cell lung cancer, the following anticipated risks are identified in the IRB application due to this clinical trial:

Serious:

- diarrhea (<10%)
- nausea, vomiting (<5%)
- precipitation of cystine, oxalate, or urate crystals resulting in kidney damage or failure (<1%)

Mild:

- dry mouth / thirst (this happens in about 45% of those receiving high-dose ascorbate)
- headache (<5%)
- abdominal pain (<5%)
- fatigue (<5%)
- facial flushing (<5%)
- sweating (<5%)
- weakness (<5%)
- injection site irritation (< 2%)
- faintness or dizziness with rapid infusion (<5%)
- ascorbate may leak outside vein (<2%)
- risk of gout, gout-like symptoms, or exacerbation of existing gout (<2%)

Radiation sensitization:

In case radiation is needed in the for the lung cancer patients, it is anticipated that ascorbate will act as a radiation sensitizer. This could result in:

- radiation side effects being observed sooner than expected
- radiation side effects being more severe than anticipated

Radiation will not be used concurrently with ascorbate in this trial.

Imaging contrast:

A sharp increase in a subject's liver function tests have been observed when the subject received CT imaging contrast on the same day as an ascorbate infusion. Kansas (Dr. Jeanne Drisko) noted similar observations. Therefore, ascorbate and CT imaging contrast (oral or IV) will not be administered on the same day.

Stopping Rules

As a phase II study, stopping rules do not apply. If a subject dies during active study treatment:

- Trial will be placed on accrual hold until case review
- The death will be reviewed by the principal investigator, IND medical monitor, and IND sponsor (and, as applicable, treating physician)
- Adverse events, including deaths on study, will be reviewed at IND investigators' meeting.

DSMC Monitoring and Compliance

The University of Iowa's Holden Comprehensive Cancer Center is an NCI-accredited cancer center meeting comprehensive requirements. All investigator-initiated protocols will be managed and monitored by its data and safety monitoring committee (DSMC). The templated DSMP has been filed with the National Cancer Institute; some minor adjustments to accommodate individual trial requirements are allowed with DSMC approval.

Required elements

Protocol. All investigator-initiated clinical trials must list the protocol number, title, and principal investigator. Additionally, sub-investigators, co-investigators, biostatisticians, and consultants must also be listed. The protocol must contain subject selection criteria (inclusion / exclusion), stopping rules (for both individual subject and the study), anticipated risks, and expected toxicities.

Plan. All DSMPs must include an annual reporting requirement to the DSMC, subject registration in the clinical trials management system (OnCore), a plan for documenting adverse events, and a plan to document protocol deviations. The DSMP must be approved by the DSMC prior to IRB approval. The IRB will then review and approve the DSMP as filed.

Risk level

As a study conducted under an investigator-sponsored IND, this study has been assigned a risk level 4 as per the NCI filed DSMP and requires the strictest level of monitoring.

Individual trial plan

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC Chairs. Study data will be made available through OnCore.

For this clinical trial, the DSMC chair has appointed an independent physician as acting Chair, as the DSMC chair also serves as medical monitor for the investigator-sponsored IND (105715, Cullen). The acting chair is a board-certified radiation oncologist, who also serves on the University of Iowa's Biomedical IRB and is active in PRIM&R, the national IRB society.

Reporting Requirements

- A scanned copy of the completed eligibility checklist, with screening information and physician signature, will be attached in OnCore for ongoing review by DSMC staff.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the Acting Chair and staff for review.

Monitoring Requirements

The DSMC utilizes a risk-based monitoring approach. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. The trial's research records will be monitored at minimum twice per year with a minimum of 25% of subjects monitored for the entire study participation (from enrollment to completion of study intervention).

Monitoring will involve the following:

- review eligibility of patients accrued to the study,
- check for the presence of a signed informed consent,
- determine compliance with protocol's study plan,
- determine if SAEs are being appropriately reported to internal and external regulatory agencies,
- compare accuracy of data in the research record with the primary source documents,
- review investigational drug processing and documentation,
- assess cumulative AE/SAE reports for trends and compare to study stopping rules.

Routine Adverse Event Reporting

For non-serious Adverse Events, documentation must begin from the first day of study treatment and typically continue through the 30 day follow-up period after treatment is discontinued**.**

Collected information should be recorded in OnCore for that subject. Event term and grade are according to NCI's Common Toxicity Criteria (CTCAE v4), and onset and resolved dates (if applicable). For serious adverse events or events ≥ grade 3, the relationship to the study drug must be included. Documentation should occur in real time. For the purposes of documenting in OnCore, the principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

Serious Adverse Event Reporting

For any experience or condition meeting the definition of a serious adverse event (SAE; 21CFR312.32), from the first day of study treatment and typically continue through the 30 day follow-up period after treatment is discontinued.

Investigators must report to the DSMC any SAE, regardless of attribution to study drug. SAEs must be reported *via* an OnCore SAE Report within 1 business day of learning of the event.

An adverse event is considered **serious** if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (21 CFR 312.32; ICH E2A and ICH E6).

Data Monitoring and Management

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Subject registration includes the following:

- Consent date and the IRB approved consent used
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

Subject Data

In addition to the subject registration and status entered in OnCore, research staff also enter the subject study data into OnCore electronic case report forms (eCRFs) for HCCC investigator initiated studies. eCRFs are approved by the PI and statistician prior to study activation to ensure the most effective data acquisition. All information on eCRFs will be traceable to the source documents which are maintained in the subject's file or in the electronic health record (EPIC). eCRF data are expected to be entered into OnCore within 30 calendar days after a subject's study visit.

Forms Monitoring

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all mandatory fields are entered completely, accurately, and within time requirements. The assigned DSMC monitor manages the logistics associated with the data monitoring review. Once the clinical trial is identified for monitoring, the monitor arranges for a selection of cases to review from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries within the eCRF to resolve missing, incomplete and/or incorrect information. A member of the research team is expected to respond to monitoring queries within 14 business days.

This process can often identify a misunderstanding or deficiency in protocol requirements early in the study and can improve data quality.

Final Reports

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

IND 105715 (J. Cullen, sponsor) Monitoring and Compliance Plan

As an independent research trial under an investigator-sponsored IND, the sponsor has approved the following individualized monitoring plan to fulfill the requirements set forth in 21 CFR§312.50 and §312.56 in addition to ICH E6 and the FDA Bioresearch Monitoring Program's Compliance Program Guidance Manual CPGM 7348.811.

The following plan was developed after reviewing the FDA's *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013), the NIH guidance OD-00-038 *Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials,* the NCI's *Conducting Clinical Trials: Essential Elements*, and the International Conference on Harmonisation *E6: Guideline for Good Clinical Practice*, which has been listed by the FDA in the Federal Register as an accredited guidance document.

Per the FDA (August, 2013) sponsors are encouraged to "…tailor monitoring plans to the needs of the trial." The FDA also places greater emphasis on centralized monitoring than the ICH E6 document, citing that centralized monitoring as described by the FDA (August 2013) was not yet feasible when the E6 document was completed.

Centralized Monitoring (CM)

For the purposes of this study, centralized monitoring refers to timely and accurate data entry into a spreadsheet for review by the principal investigator, sponsor, and/or designee. Remote monitoring enables data to be evaluated for quality, safety, and an interim analysis in real-time. Data to be entered are those identified as critical by the principal investigator and sponsor. Critical data can be monitored remotely through centralized monitoring (FDA, 2013, page 11).

CM — critical data

- Eligibility criteria (lab values, performance status, date of G6PD result, date of 15g test dose)
- Baseline constitutional assessments performed and graded (Y/N)
- Labs at day 1 of each cycle ordered and reviewed (Y/N)
- Constitutional assessments performed and graded at start of each cycle (Y/N)
- Subject temperature at pre-infusion, hourly during, and post-infusion
- List of adverse events, with CTCAE grading, collected from infusion to +21 days post-infusion with codified attribution as appropriate

CM — frequency of entry and review

Centralized data will be entered within 2 weeks of the ascorbate infusion. Data will be reviewed no less than quarterly by the PI, sponsor, or designee. Email or written documentation of review will be sent to the sponsor or the sponsor's designee. Alternatively, review can be performed or confirmed at sponsor-directed IND meetings.

On-Site Monitoring (On-Site)

Additional monitoring may be ordered by the principal investigator or sponsor. The principal investigator may select the monitor for the study but final approval must be obtained from the sponsor prior to any monitoring activities.

On-Site— critical data

At minimum, the outside monitor will review the protocol against the provided monitoring sheet. Additional data to be reviewed may be added at the request of the sponsor, the sponsor's designee, the principal investigator, or the principal investigator's designee.

On-Site — frequency of review

Frequency of review (in addition to the monitoring provided by the HCCC monitoring plan) will be determined by quality audits performed by the sponsor or sponsor's designee.

On-Site — reports

Monitoring reports will comply with ICH *E6* and the FDA's *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013). Finalized reports will be submitted to the sponsor, the principal investigator, the principal investigator's designee, and the sponsor's designee within 30 calendar days of the on-site monitoring visit. A copy of the final report, and any corrective action plans, will be submitted to the institutional review board.

Auditing

> The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.
>
> To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.
>
> ~ International Conference on Harmonisation, *E6*

The sponsor intends to comply with auditing procedures to evaluate conduct and compliance with protocol, SOPs, GCP, and the DSMP filed with this protocol. Audit findings will be disseminated and discussed at quality meetings by the sponsor.

PROTOCOL APPENDIX D: RECOMMENDED MONITORING WORKSHEETS

Consent

Subject ID: _____

Date of consent: _____

Version signed ICF (mm/dd/yy): _____

Valid ICF date (mm/dd/yy): _____ [from HawkIRB application]

Valid ICF [Y/N]:_____

Eligibility

1. Histologically/cytologically diagnosed NSCLC: _____
2. Staged IIIB, IV, or recurrent: _____
3. At least 18 years:_____
4. ECOG 0, 1, or 2:_____
5. G6PD deficiency [N]:_____
6. Hemoglobin ≥ 8g/dL (21d ≤ C1D1) _____
7. ANC ≥ 1500 / microL (21d ≤ C1D1) _____
8. Platelets at least 100k / microL (21d ≤ C1D1)_____
9. Creatinine ≤ 1.5 x ULN (21d ≤ C1D1):_____
10. T. Bili ≤ 1.5 x ULN (21d ≤ C1D1):_____
11. ALT ≤ 3x ULN (21d ≤ C1D1): _____
12. AST ≤ 3x ULN (21d ≤ C1D1): _____
13. Negative serum pregnancy test WCOBP: _____
14. Actively receiving warfarin [N]:_____
15. Actively receiving insulin [N]: _____
16. Known EGFR or ALK gene abnormality unless treatment progression [N]: _____
17. Known hemoptysis [N]:_____
18. Receiving brain radiation therapy [N]: _____
19. On flecainide, methadone, amphetamines, quinidine, or chlorpropamide [N]: _____

20. Known active invasive malignancy other than NSCLC [N]: _____
    (exceptions: non-melanoma skin cancers or carcinoma *in situ* of the cervix or bladder)

21. Other investigational agents with an intent to treat [N]: _____

22. Concurrent illnesses clause [N]: _____

23. Known HIV positive status [N]: _____

Eligibility confirmed [Y/N/NA]: _____

Subject ID & initials: _____

Baseline Assessments

These assessments should be done within 21d of C1D1. Assessments may be completed C1D1 before therapy.

Mark the below Y/N

Con meds reviewed	_____	Temperature	_____
Blood pressure	_____	Heart rate	_____
Weight	_____		_____

Mark the below Y/N. To mark yes, each symptom should be have a grade

Fatigue	_____	Neuropathy	_____
Infection	_____	Nausea	_____
Vomiting	_____	Pain (headache)	_____

Mark the below Y/N. Labs can be screening (if $\leq$ 21 days of C1D1) or drawn on C1D1

CBC w/diff	_____	Creatinine	_____
Potassium	_____	T. Bilirubin	_____
BUN	_____	AST	_____
ALT	_____	Alk Phos	_____
Albumin	_____	Glucose	_____
Calcium	_____	Sodium	_____
Chloride	_____	CO2	_____
Uric Acid	_____		_____

Cycle 1

Labs. Drawn up to 1 week prior. Mark the below Y/N

CBC w/diff		Creatinine	
Potassium		T. Bilirubin	
BUN		AST	
ALT		Alk Phos	
Albumin		Glucose	
Calcium		Sodium	
Chloride		CO2	

Constitutional. Mark the below Y/N. To mark yes for symptoms they must have a grade

Fatigue		Neuropathy	
Infection		Nausea	
Vomiting		Pain (headache)	
History / Physical		Other	

Infusion assessments. Mark the below Y/N/NA. Assessments should be done pre- and post-infusion. Hourly only as clinically indicated. (protocol section 6.3)

	Cycle Infusion Number					
	1	**2**	**3**	**4**	**5**	**6**
Pre-infusion						
Post-infusion (≤15 min EOI)						

Paclitaxel. Complete as prompted. Actual height and weight from day of infusion should be used per protocol. Dosing is 200 mg/m^2 (5.3.3.)

Date, day 1		Actual height	
Dose infused		Actual weight	
Dose modified [Y/N]		Actuals used [Y/N]	

Carboplatin. Complete as prompted. (5.3.3.)

Date, day 1		After paclitaxel?	
Dose modified [Y/N]			

Cycle 2

Labs. Drawn up to 1 week prior to D1. Mark the below Y/N

CBC w/diff		Creatinine	
Potassium		T. Bilirubin	
BUN		AST	
ALT		Alk Phos	
Albumin		Glucose	
Calcium		Sodium	
Chloride		CO2	

Constitutional. Mark the below Y/N. To mark yes for symptoms they must have a grade

Fatigue		Neuropathy	
Infection		Nausea	
Vomiting		Pain (headache)	
History / Physical		Other	

Infusion assessments. Mark the below Y/N/NA. Assessments should be done pre- and post-infusion. Hourly only as clinically indicated. (protocol section 6.3)

	Cycle Infusion Number					
	1	**2**	**3**	**4**	**5**	**6**
Pre-infusion						
Post-infusion (≤15 min EOI)						

Paclitaxel. Complete as prompted.. Dosing is 200 mg/m^2 (5.3.3.)

Date, day 1			
Dose infused			
Dose modified [Y/N]		Actuals used [Y/N]	

Carboplatin. Complete as prompted. (5.3.3.)

Date, day 1		After paclitaxel?	
Dose modified [Y/N]			

MRI / CT ordered post cycle 2 [date]: _____

Cycle 3

Labs. Drawn up to 1 week prior. Mark the below Y/N

CBC w/diff		Creatinine	
Potassium		T. Bilirubin	
BUN		AST	
ALT		Alk Phos	
Albumin		Glucose	
Calcium		Sodium	
Chloride		CO2	

Constitutional. Mark the below Y/N. To mark yes for symptoms they must have a grade

Fatigue		Neuropathy	
Infection		Nausea	
Vomiting		Pain (headache)	
History / Physical		Other	

Infusion assessments. Mark the below Y/N/NA. Assessments should be done pre- and post-infusion. Hourly only as clinically indicated. (protocol section 6.3)

	Cycle Infusion Number					
	1	**2**	**3**	**4**	**5**	**6**
Pre-infusion						
Post-infusion (≤15 min EOI)						

Paclitaxel. Complete as prompted.. Dosing is 200 mg/m^2 (5.3.3.)

Date, day 1			
Dose infused			
Dose modified [Y/N]		Actuals used [Y/N]	

Carboplatin. Complete as prompted. (5.3.3.)

Date, day 1		After paclitaxel?	
Dose modified [Y/N]			

Cycle 4

Labs. Drawn up to 1 week prior. Mark the below Y/N

CBC w/diff		Creatinine	
Potassium		T. Bilirubin	
BUN		AST	
ALT		Alk Phos	
Albumin		Glucose	
Calcium		Sodium	
Chloride		CO2	

Constitutional. Mark the below Y/N. To mark yes for symptoms they must have a grade

Fatigue		Neuropathy	
Infection		Nausea	
Vomiting		Pain (headache)	
History / Physical		Other	

Infusion assessments. Mark the below Y/N/NA. Assessments should be done pre- and post-infusion. Hourly only as clinically indicated. (protocol section 6.3)

	Cycle Infusion Number					
	1	**2**	**3**	**4**	**5**	**6**
Pre-infusion						
Post-infusion (≤15 min EOI)						

Paclitaxel. Complete as prompted. Dosing is 200 mg/m^2 (5.3.3.)

Date, day 1			
Dose infused			
Dose modified [Y/N]		Actuals used [Y/N]	

Carboplatin. Complete as prompted. (5.3.3.)

Date, day 1		After paclitaxel?	
Dose modified [Y/N]			

MRI / CT ordered post cycle 4 [date]: _____

Regulatory Review

Adverse Events. Obtain a copy of the adverse event log. Determine if adverse events are recorded and reported per protocol:

Reporting

Table 2: CTEP/NCI's Recommended Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention (Phase 1 and Early Phase 2 Studies)[1]

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Adverse events that are not deemed serious are reported through routine adverse event requirements.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

Effective Date: May 5, 2011

Deviations. Obtain a copy of the deviation log. Determine if deviations are recorded and if they are reported to the UIOWA IRB per policy:

Immediate deviation reporting:

(1) subject safety (reportable AE per HSO definitions),

(2) a change to the ICF, or

(3) a risk to be communicated to other enrolled subjects

For all other deviations (which would be considered procedural deviations), the IRB requests that they be collected on an excel spreadsheet and then submit them at the time of a continuing review.