Adjunctive **I**ntra**v**enous **A**scorbic **A**cid (AIVAA) for Advanced Non-Small Cell Lung Cancer: A Double Blind, Placebo Controlled, Phase II Randomized Controlled Trial

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PROTOCOL SIGNATURE PAGE

Investigator's Agreement:

I confirm that I have reviewed and agree to the conditions delegated to me relating to the above-mentioned protocol. I acknowledge that I have read the protocol entitled *Adjunctive Intravenous Ascorbic Acid for Advanced Non-Small Cell Lung Cancer: A Double Blind, Placebo Controlled, Randomized Controlled Trial* (version date: January 19th, 2026) and agree to carry out its terms in accordance with the approved protocol, Part C, Division 5 of the Food and Drug Regulations, and ICH GCP guidelines for good clinical practice.

_____	_____	_____
Signature	Qualified Investigator (please print)	Date
_____	_____	_____
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1 Background

Lung cancer is the leading cause of cancer-related mortality for both men and women in Canada, accounting for 26% of cancer deaths. An estimated 28,600 new cases of lung and bronchus cancer were diagnosed in 2017. While the five-year survival rate has improved over the past few decades, lung cancer survival remains low, especially for cases detected at later stages. For instance, estimates of five-year survival rates for non-small cell lung cancer (NSCLC) in the United States range from a dismal 1-10% for stage IV to 68-92% for stage I. For small cell lung cancer (SCLC), the rates are even bleaker: 2% for stage IV and 31% for stage I.[1] In Canada, the overall 5-year survival for all stages is 17%, compared to 95% for prostate cancer and 85% for breast cancer (Canadian Cancer Society statistics).

Surgery remains the cornerstone of curative intent treatment for thoracic malignancies. However, approximately half of all lung cancers diagnosed in 2017 were stage IV and thus not eligible for surgical resection.[1] For patients with incurable advanced or metastatic lung cancer, radiation, chemotherapy or immunotherapy is the first line of treatment, with the exception being a small proportion who harbor a targetable oncogenic driver mutation.

Front-line therapy for incurable stage IIIB and IV NSCLC is typically a cisplatin or carboplatin-based doublet wherein toxicity is known to be high and may lead to mortality. Chemotherapy related patient-reported side effects, such as fatigue, nausea and vomiting, and loss of appetite are common.[2] While immunotherapy provides a promising new paradigm of treatment for many patients, platinum-doublet chemotherapy remains the first or subsequent option for the majority of patients with incurable lung cancer.[1,3,4] Innovations in lung cancer therapy that improve outcomes and reduce toxicity are clearly needed.

Intravenous vitamin C (IVC) is a frequently used adjunctive therapy among naturopathic doctors and other integrative oncology health care practitioners. In the 1970s, Linus Pauling, along with Ewan Cameron, published preliminary case series and uncontrolled trials showing longer survival times among advanced cancer patients treated with IVC.[5,6] While the weak methodology of this research has been criticized, these early studies generated considerable interest in vitamin C as a therapeutic agent for enhancing the efficacy of chemotherapy and reducing associated side effects. More recently, pre-clinical and clinical studies have explored the impact of IVC on tumour mass, quality of life (QOL) and mitigation of side effects from chemotherapy,[7-11] including a recent study with a population of NSCLC patients receiving platinum doublet chemotherapy.[12] While results have been promising, most clinical trials performed to-date have been small single arm, open-labelled and highly susceptible to bias.

Despite the lack of robust evidence of clinical efficacy, practitioners of complementary and alternative medicine administer high dose IVC to numerous lung cancer patients across Canada and globally in hopes that it synergizes the anti-cancer effects of chemotherapy, reduces its

toxicity, and improves survival. Moreover, patients are paying out-of-pocket for IVC treatments. While controversy remains around the use of high dose ascorbic acid in cancer patients, most studies show an improvement QOL measurements such as fatigue, nausea, pain, and loss of appetite.[13] The positive impact on QOL perhaps stems most from the amelioration of toxic side effects associated with chemotherapy.

We are proposing the world's first double-blind, randomized, placebo-controlled trial to evaluate the impact of IVC in conjunction with chemotherapy on quality of life, toxicity and survival amongst patients with incurable non-small cell lung cancer.

1.1 Ascorbic Acid

Ascorbic acid is a six-carbon carbohydrate and a required co-factor for 17 different hydroxylase enzymes. Humans have a mutated gene encoding for the synthesis of ascorbic acid, making vitamin C an essential nutrient for life. The bioavailability of vitamin C is regulated through intestinal absorption, tissue stores, renal resorption and excretion, and health status. The total human body store of vitamin C can range between 30 mg (at severe depletion such as scurvy) and 2 g but normally ranges between 0.70-1.4 mg/dL in the blood plasma. Oral consumption of vitamin C creates maximal serum levels of 1.3-4.0 mg/dL. Once plasma ascorbic acid concentrations reach saturation from oral doses (100-150 uM), excess ascorbic acid is excreted in the urine. Intravenous administration bypasses the intestinal absorption system, allowing plasma concentrations to increase above 350 mg/dL (>20 mM), levels unattainable via oral administration.[13]

1.2 Mechanism of Action of Ascorbic Acid in Cancer

Past studies have administered ascorbic acid via oral and/or IV routes, making it difficult to interpret its anti-tumour effect and impact on chemotherapy-related toxicity. Recent studies have explored the possible mechanisms of action of IVC and demonstrated its therapeutic effects to be biologically plausible. In vitro experiments have shown that administering ascorbic acid in pharmacologic doses kills cancer cells but does not harm normal cells. The mechanism posited is via hydrogen peroxide formation in the extracellular fluid around normal and tumour tissues caused by pharmacologic doses of ascorbic acid. In normal cells, hydrogen peroxide is metabolized to water and oxygen by the enzyme catalase. Because cancer cells typically lack catalase, they are vulnerable to the cytotoxic effects of hydrogen peroxide, resulting in preferential cytolytic activity with high doses of serum ascorbic acid.[14-16]

In breast cancer patients, adjunctive ascorbic acid to chemotherapy using adriamycin or cyclophosphamide inhibits tumour growth, compared to using either chemotherapeutic agent alone.[16] The exact mechanisms for ascorbic acid's effects in conjunction with chemotherapy are currently unknown; however, it has been postulated that ascorbic acid increases the cellular reactive oxygen species (ROS) concentrations in cancer cells, or lowers cellular antioxidant

defenses by altering levels of glutathione peroxidase I (GPX-1) or glutathione (GSH) in cancer cells.[17,18] Cancer cells have antioxidant mechanisms and thus require higher doses of reactive oxygen species generating chemotherapeutics to be effectively destroyed.[19,20]

1.3 Efficacy

A 2014 pilot randomized controlled trial (RCT) investigated the use of high-dose (75-100 g) IVC twice weekly for 12 months in 27 women with stage III-IV ovarian cancer in conjunction with paclitaxel and carboplatin chemotherapy.[10] The study found that women who received IVC treatment reported significantly reduced side effects related to chemotherapy in almost all categories of toxicity, including in neurological, bone marrow, infectious, hepatobiliary & pancreatic, renal & genitourinary, pulmonary, gastrointestinal and dermatological systems. Women receiving IVC reported less than half the average number of grade I and II adverse events per visit compared to the control group. Median time to disease progression or relapse was 8.8 months longer in the IVC group (25.5 vs 16.8 months). The study was not powered for disease progression and the improvement seen in this outcome was not statistically significant.

Two studies assessing tumour response to IVC produced different results.[21,22] One reported no objective tumour response among 17 patients with solid tumours when 100-220 g IVC was given four times weekly for four weeks as monotherapy. The other study reported a decrease in tumour size by 10-42% in eight out of nine patients with metastatic pancreatic cancer when IVC 50, 75, or 100 g was given three times weekly for eight weeks, alongside gemcitabine and erlotinib.[22] Thus, IVC as monotherapy for cancer is not supported.

We have published a systematic review in 2014 of IVC use in cancer patients looking at its efficacy and found that out of a total of 37 studies, there were: 2 open-label RCTs, 15 uncontrolled trials, 6 observational studies and 14 case reports.[16] IVC dosing ranged from 1 - 200 g per infusion and was typically administered 2-3 times weekly. IVC did not increase toxicity or interfere with the antitumor effects of the chemotherapeutic agents (i.e., gemcitabine and erlotinib or paclitaxel and carboplatin) in any of these studies. Data from one RCT and uncontrolled human trials found improvement in survival rate and time to relapse, as well as a reduction in tumor mass. Case reports documented several instances of tumor regression and long-term disease-free survival associated with use of IVC. Adjunctive IVC also improved measures relating to quality of life, physical function, and toxicities associated with chemotherapy, including fatigue, nausea, insomnia, constipation, and depression.

1.4 Safety

Phase I studies of IVC alone and in conjunction with chemotherapy have reported excellent safety profiles.[5,8,10,21-26] A survey of providers who used IVC for 9,328 patients reported an AE rate of 1.0%.[27] Reported side effects of IVC used in clinical trials include nausea, dizziness, dry mouth, perspiration, and weakness.[21,26]

While caution is typically advised for the use of IVC in cancer patients with end-stage renal failure predisposed to oxaluria,[28,29] two studies suggested that IVC (0.3 and 0.5 g) can be safely used to mobilize iron stores and increase hemoglobin levels in patients with functional anemia without any increased risk for renal stones.[30,31] Several case reports have referenced vitamin C intake as a possible cause of renal stone formation in patients with hyperoxaluria.[32,33] No prospective trials have supported this link.[34,35] The main recognized toxicity is hemolysis in patients with a deficiency in glucose 6 phosphate dehydrogenase (G6PD).[36,37] Testing for G6PD deficiency before IVC administration is therefore required prior to providing doses higher than 15 g.

Pre-clinical and clinical evidence repeatedly demonstrates that ascorbic acid does not reduce the effectiveness of chemotherapy.[16] The majority of adverse effects reported in clinical trials involving intravenous vitamin C seem largely attributable to chemotherapy.

1.5 Rationale for current study

With an apparently excellent safety profile, as well as pre-clinical and clinical evidence suggesting a plausible anti-tumour effect and reduction in chemotherapy-related toxicity, this relatively inexpensive non-patented agent warrants closer examination. In addition to the need for more rigorously designed studies, there are significant cost implications for patients receiving IVC, especially in a publicly funded health care system that exists in Canada.

Canadian patients are paying out of pocket for this therapy at rates that are often prohibitive to the public. An online search revealed that infusion costs range between $102 and $331 per session and are often recommended 2-3 times weekly for up to six months in duration. Total costs to patients range from a few hundred dollars to trial the therapy to $20,000 or more for continued therapy in certain scenarios. Within this context and with clear equipoise, there is an urgent need for a rigorously controlled and blinded study to determine whether IVC has a role in lung cancer therapy in conjunction with chemotherapy for quality of life, disease progression, and survival.

2 Objectives and Hypothesis

2.1 Objectives

2.1.1 Primary objective

To assess the impact of IV ascorbic acid on patient quality of life during first line platinum-doublet chemotherapy for patients with stage IIIB or IV non-small cell lung cancer.

2.1.2 Secondary objectives

(1) To assess the effect of supplementing platinum-doublet chemotherapy with IVC on chemotherapy-related toxicities

(2) To assess the frequency in both arms of having to discontinue chemotherapy treatment due to excess toxicity

(3) To assess the effect of IVC on general symptom burden

(4) To assess changes in inflammatory markers in each study arm

(5) To assess the effect of supplementing platinum-doublet chemotherapy with IVC on tumour progression and survival

(6) To assess the safety and tolerability of administering IVC acid alongside platinum-doublet chemotherapy

2.2 Hypothesis

The addition of IV ascorbic acid to platinum-doublet chemotherapy in patients with incurable non-small cell lung cancer will improve QOL, reduce toxicity, reduce inflammatory cytokines, slow tumour progression, and improve survival compared to a placebo.

3 Study Design

3.1 Study Overview

We propose a two arm, parallel group, double-blind, placebo-controlled, phase II randomized controlled trial. Eligible patients will be randomly assigned using a web randomization system in a 1:1 ratio to one of the following two interventions: (1) Standard platinum-doublet chemotherapy and IV placebo twice a week or (2) standard platinum doublet chemotherapy and IVC twice a week. IVC or placebo will be given as an adjunct throughout chemotherapy and continue until disease progression or 6 months post-randomization.

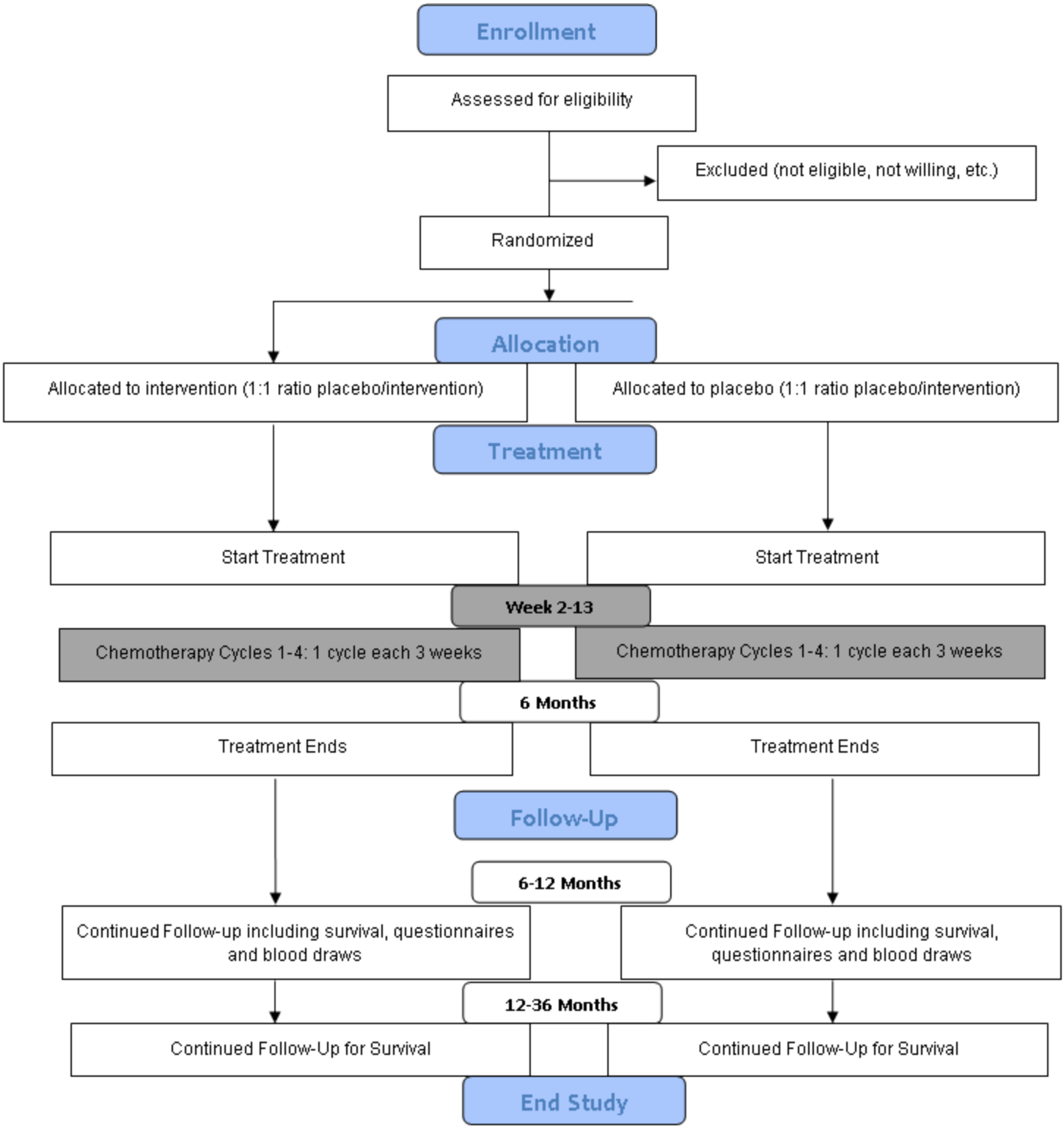


Figure 1: Patient flow through the trial, according to enrollment and timeline

3.2 Participants

Patients with lung cancer will be screened and recruited at The Ottawa Hospital Cancer Centre (TOHCC), the central point of referral for patients with lung cancer in Ottawa and the surrounding region. There are approximately 600 cases of lung cancer diagnosed and seen at TOH annually. Nearly half of these have stage IIIB and IV NSCLC at diagnosis, and about 60% will receive first line platinum doublet chemotherapy. Based on experience, the intensity of the treatment regime planned, and the placebo control, we anticipate being able to recruit approximately 20 to 25 participants per year.

3.3 Eligibility Criteria

3.3.1 Inclusion criteria

1. Adults (≥18 years of age) seen at TOHCC with stage IIIB or IV primary non-small cell lung cancer
2. Eligible and scheduled for first line platinum-doublet chemotherapy with or without concurrent immunotherapy

3.3.2 Exclusion criteria

1. ECOG status greater than 2
2. Previously received IVC within 6 months prior to randomization
3. Biochemical deficiency in G6PD
4. Estimated Glomerular Filtration Rate (eGFR) less than 45 mL/min
5. Currently taking insulin or warfarin
6. History of severe renal dysfunction or hemochromatosis
7. Previously undergone cytotoxic chemotherapy or immunotherapy within 12 months prior to randomization
8. If pregnant or planning to become pregnant: not a carrier of the gene for G6PD deficiency
9. Currently taking an investigational product or participation in an investigational study within the past 30 days
10. Any reason which, under the discretion of the Principal Investigator or delegate, would preclude the patient from participating

3.4 Interventions

The interventions for this study will be vitamin C in sterile water for those in the treatment arm and normal saline for those in the control arm. Exact formulations for the study interventions are as follows:

Vitamin C

Formulation: Solution. Please see table 1 for exact amounts of IVC and sterile water.

Dose: 1 gram per kilogram body weight twice weekly for 6 months. The full dose escalation is outlined in section 4.6.

Vitamin C is supplied by Viatris at a concentration of 500 mg/mL. Sterile Water is supplied by The Stevens Medical Company in 250mL, 500mL, or 1000mL bags.

Normal Saline

Formulation: 0.9% Sodium Chloride solution.

Dose: An equivalent volume to what would be given if the participant was in the treatment arm. Please see table 1 for exact amounts of normal saline.

Normal Saline is supplied by The Stevens Medical Company in 250mL, 500mL, or 1,000mL bags.

Table 1: Information Regarding Investigational Drug Preparation and Dispensation

Vitamin C Dose (g)	Volume Vitamin C (mL)	Volume Sterile Water (mL)	Total Volume (mL)[1]	Osmotic Content (mOsm*vol)	Infusion Time (min)	Vitamin C infusion rate (g/min)
15	30	220	250	696	30	0.50
50	100	400	500	1160	100	0.50
55	110	390	500	1276	110	0.50
60	120	880	1000	696	120	0.50
65	130	870	1000	754	130	0.50
70	140	860	1000	812	140	0.50
75	150	850	1000	870	150	0.50
80	160	840	1000	928	150	0.53
85	170	830	1000	986	150	0.57
90	180	820	1000	1044	150	0.60
95	190	810	1000	1102	150	0.63
100	200	800	1000	1160	150	0.67

1 – Participants in the control arm will receive saline equal to the total volume. Gtts: drops

3.5 Outcome Measures and Timeline

3.5.1 Quality of Life (Primary Outcome)

QOL will be assessed using the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire. FACT-L measures QOL using 5 sub scales: physical, social, emotional, and functional wellbeing, plus a subsection on symptoms specific to lung cancer. FACT-L is scored using the general score (FACT-G), which includes physical, social, emotional, and functional scales, the trial outcome index (TOI), which includes the physical, functional, and lung cancer symptom (LCS) scales, and total score (FACT-T), which includes all scales. All patients will complete the FACT-L at baseline and then at the onset of the first four chemotherapy cycles, 6M, and 12M. The primary endpoint will be the difference in TOI score at 6 months.

3.5.2 Chemotherapy-Related Toxicities

Patients will report the incidence and severity of adverse events via the companion Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE). We have developed a version of the PRO-CTCAE specifically for advanced lung cancer patients receiving chemotherapy that assesses the frequency, severity, and interferences of 31 symptomatic treatment toxicities. Adverse events will be assessed at baseline and then at the onset of the first four chemotherapy cycles, 6M, and 12M.

3.5.3 Discontinuation frequency for chemotherapy

The frequency of delayed or missed chemotherapy sessions, as well as the reason(s) for discontinuation, will be documented in both arms throughout the duration of chemotherapy including the overall duration of chemotherapy each participant receives.

3.5.4 General Symptom Burden

General symptom burden will be captured using the Edmonton Symptom Assessment Scale (ESAS). The ESAS has 9 distinct symptoms common to patients with cancer plus one additional “other” symptom. Each is on a scale of 1-10 for a total score of 0-100. ESAS will be measured alongside FACT-L and the PRO-CTCAE at baseline, at the onset of the first four chemotherapy cycles, 6M, and 12M.

3.5.5 Immune and Inflammatory markers

Blood work will be completed at baseline, at the 4th chemo cycle, 6M and 12M to assess patients’ complete blood count (CBC) with differential and level of high sensitivity C-reactive protein (hsCRP).

3.5.6 Progression and Survival

Response rate to chemotherapy as measured using RECIST 1.1 criteria will be documented at baseline, the third chemotherapy cycle, 6 months, and 1, 2, and 3 years. One, two, and three-

year survival rate after treatment conclusion will also be collected. Date of death will be ascertained to allow calculation of median survival.

3.5.7 Safety

Safety will be monitored by collection of adverse events and serum creatinine. The frequency and reasons for discontinuation of the study drug (e.g., adverse reaction to infusion, unsafe creatinine levels) will be compared between arms. Adverse events will be assessed before, during, and after administration of the study drug by an investigator or delegate; creatinine will be collected at baseline and at the onset of each chemotherapy cycle at TOHCC as part of standard of care, and each 3 weeks by the CHI upon completion of chemotherapy for the remainder of the intervention period. Any unscheduled blood draws (see section 3.6.1) will take place at the CHI and will be analyzed by Dynacare.

Table 2: Schedule of Events

Event	Time Point													
	Screening	Baseline[2]	Chemo Cycle 1	Chemo Cycle 2	Chemo Cycle 3	Chemo Cycle 4	Week 15	Week 18	Week 21	Week 24	6 Months	12 Months[2]	24 Months	36 Months
Eligibility Assessment[1]	✓													
Informed Consent	✓													
Medical History & Physical Exam		✓												
Concomitant Medications		✓	---------- **Continuous** ----------											
Study Treatment			Twice Weekly →											
hsCRP, CBC		✓				✓					✓	✓		
Creatinine[3]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
RECIST Assessment		✓			✓						✓	✓	✓	✓
FACT-L		✓	✓	✓	✓	✓					✓	✓		
PRO-CTCAE		✓	✓	✓	✓	✓					✓	✓		
ESAS		✓	✓	✓	✓	✓					✓	✓		
Assessment of Adverse Events			---------- **Continuous** ----------											

Chemo: Chemotherapy. FACT-L: Functional Assessment of Cancer Therapy – Lung. ESAS: Edmonton Symptom Assessment Scale. PRO: Patient Reported Outcomes. CTCAE: Common Terminology Criteria for Adverse Events. RECIST: Response evaluation criteria in solid tumours. Outcomes at the onset of the first 4 chemotherapy cycles will be completed between 3 and 10 days after the first infusion of the cycle. Any tests not conducted as part of standard of care will be performed at the Centre for Health Innovation.

[1] Includes blood G6PD and eGFR [2] These time points require a visit with a naturopathic doctor. [3] Part of standard of care while receiving chemotherapy. If not receiving chemotherapy, creatinine will be collected by the Centre for Health Innovation at weeks 15, 18, 21, and 24.

3.6 Premature Withdrawal and Discontinuation Criteria

Participants will be free to withdraw from the study at any time. If a participant wishes to withdraw, a participant withdrawal form will be completed by the research staff indicating the participant has withdrawn and whether consent is given to ongoing chart review by the study team. We will follow withdrawn participants for progression and survival up to 3 years post-randomization should they consent. Investigators will withdraw participants from the study for the following reasons:

- The participant starts taking exogenous IVC.
- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that the investigator believes continued participation in the study would not be in the best interest of the participant.

Investigators will discontinue the study intervention for participants for the following reasons:

- The participant starts taking insulin or warfarin.
- The participant's ECOG status deteriorates to 3 or 4.
- The participant's eGFR drops below 45 mL/min.
- The participant cannot tolerate the study treatment.
- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that the investigator believes continued use of the intervention would not be in the best interest of the participant.

Participants who plan to become pregnant while on-study must hold study infusions until they have undergone genetic testing for G6PD. If they are a carrier for deficiency, the study treatments will be discontinued. All participants will be followed for at least 1 month after treatments end for AEs as outlined in section 7. If the study intervention is stopped, the participant may decide to continue their active participation in the study (i.e., complete questionnaires and have their blood drawn) or withdraw their participation. For those who withdraw from the study, they will also be asked if the research team may continue to collect data from their medical records as stated above. Participants who withdraw/are withdrawn from the study will not be replaced.

3.6.1 Monitoring of Acute Kidney Injury (AKI)

As there is a safety concern for acute oxalate nephropathy (AON), participants will be subject to increased monitoring based on their serum creatinine and eGFR levels as follows:

For participants with screening eGFR ≥ 60 mL/min:

- No additional monitoring required

For participants with screening eGFR between 45 and 59 mL/min:

- Monitoring of serum creatinine once weekly for the first three weeks. If serum creatinine does not increase by more than 1.5 times baseline or 26.5 µmol/L, monitor as per protocol. Otherwise, continued monitoring weekly. Re-assess each 3 weeks.

For participants whose serum creatinine rises 1.5-1.9 times baseline or 26.5 µmol/L:

- Temporary interruption of investigational product pending clinical assessment by an investigator
- At the discretion of the investigator, repeat testing within 1 week of assessment. Re-start investigational product if levels fall below 1.5 times baseline. Otherwise, continue hold on study drug until next routine creatinine assessment.
- If testing is not warranted, administration of investigational product to continue

For participants whose serum creatinine rises 2.0 or more times baseline:

- Permanent removal from the study
- Clinical evaluation by an investigator for AKI and repeat creatinine testing within 1 week
- At the discretion of the investigator, continued clinical assessments and testing each 2 weeks
- Referral to nephrology at the discretion of the investigator

3.7 Concomitant Medications

Participants will receive all usual medications prescribed by their treating oncologist (or other MD) for the duration of the trial. Information on concomitant medications will be gathered as outlined in Table 2. There are no medications or natural health products that have an absolute contraindication with IVC. Participants will not be permitted to receive exogenous IVC infusions until they have reached the 1-year time point, and will be withdrawn from the study per section 3.6 if they do.

4 Study Conduct

4.1 Ethical Considerations and Study Oversight

Ethical approval for this study will be sought from Research Ethics Boards (REB) of the Ottawa Health Sciences Network (OHSN) and Canadian College of Naturopathic Medicine (CCNM). Renewals will be submitted and approved annually by each REB. The protocol, informed consent form, recruitment materials, and all participant materials will receive approval from both REBs prior to any participant being enrolled. This trial will also be submitted to the Pharmaceutical Products Directorate (PPD) of Health Canada. The trial will be registered on clinicaltrials.gov and updated regularly as per ethical requirements.

This study will be conducted according to the Canadian and international standards of Good Clinical Practice (GCP) and the Health Canada Food and Drug Act, Part C, Division 5: Drugs for Clinical Trials Involving Human Subjects. All essential and regulatory documents will be stored using Clinical Research IO (CRIO) eRegulatory software. CRIO eRegulatory is compliant with the Code of Federal Regulations title 21, section 11: Electronic Records and Signatures. A validation plan and standard operating procedures will be maintained by the study team. No patient information will be stored on CRIO.

4.2 Quality Control and Quality Assurance

4.2.1 Monitoring

As per the study monitoring plan, the trial will have a quality control monitoring process in place to verify that all data are accurate and complete. Site investigators will permit trial-related monitoring, audits and regulatory inspections, and direct access to source data/documents. The monitor will generate a site monitoring report for the site investigator to detail significant findings, deviations, deficiencies, plausibility, record completeness and any corrective actions to be taken. Full information can be found in the study monitoring plan.

4.2.2 Standard Operating Procedures (SOP)

Each site will follow their individual institutional SOPs. A Procedures Manual will be developed for study-specific procedures prior to the study starting. These documents will be used to facilitate study conduct and training.

4.2.3 Adherence to the Protocol

Protocol Amendments: All amendments to this protocol will be reviewed by both REBs and submitted to the TPD as either a Clinical Trial Notification or a Clinical Trial Application Amendment. Each principal investigator will sign the approved protocol prior to implementation, and each investigator and member of the research team will be adequately trained prior to carrying out and study-specific tasks after the approval of the amendment.

Protocol Deviations: No deviations from this protocol will be permitted without the prior written approval of the Sponsor, except when the modification is needed to eliminate an immediate hazard or hazards to participants. Any deviations that may affect a participant's treatment or informed consent, especially those increasing potential risks, will receive prior approval from both REBs unless performed to remove an immediate safety risk to the participants. In this case they will be reported to both REBs immediately thereafter. Any departures from the protocol will be documented in the participant's file.

4.3 Recruitment and Assessment of Outcomes

Screening and recruitment for this study will be done at The Ottawa Hospital Cancer Centre. Medical oncologists (those who are co-investigators) will approach eligible participants to obtain consent to contact. An investigator or delegate will then conduct the informed consent process if the patient is interested in the study. If interested, the patient must undergo a blood G6PD test and a pregnancy test (if they are of childbearing potential). The medical oncologist will then confirm eligibility and write the study prescription. Randomization will occur thereafter. Adverse events will be periodically assessed by researchers at TOHCC and the CHI. All subsequent study assessments and treatments will be completed at the CHI. All participants will receive standard-of-care chemotherapy with platinum-doublet, as chosen by the treating oncologist, in addition to the interventions. Chemotherapy and associated procedures will be administered as per standard of care at The Ottawa Hospital Cancer Centre or a satellite facility.

4.4 Informed Consent

All participants for this study will be provided a consent form describing the study and providing sufficient information for participants to make an informed decision about their participation. Each participant will have sufficient opportunity to discuss the study, have all their questions addressed and consider the information in the consent process prior to agreeing to participate. This consent form will be signed and dated by the participant and the investigator or delegate obtaining the consent prior to the completion of any study activities, including screening tests for G6PD and eGFR. The original signed informed consent form will be retained in the participant's study files and a copy will be provided to the participant.

4.5 Randomization

Randomization will occur upon receiving confirmation that the patient meets all eligibility criteria and their G6PD and eGFR are within the limits outlined for eligibility. Patients who are pregnant, or who plan on becoming pregnant, must additionally undergo genetic testing for G6PD to ensure they are not a carrier of the gene for deficiency. Patients who consent to participate whose results would preclude participation will not be randomized and will be marked as screen failures.

4.6 Chemotherapy Procedure

Chemotherapy schedules and administration will take place as per the standard of care at The Ottawa Hospital Cancer Centre under the guidance of the treating oncologist. As adherence to chemotherapy is part of our outcomes, missed or delayed chemotherapy visits will not be marked as protocol deviations. All patients will be scheduled to receive 4 cycles of chemotherapy. Cycles 5 and 6 are optional and may be added at the discretion of the treating oncologist.

4.7 Intervention Procedure

A qualified healthcare provider will administer either IVC or placebo infusion two times weekly until disease progression or 6 months post-randomization. Dosage for ascorbic acid will be set at 1 g per kg of body weight. This dose was chosen as it has been shown to reach cytotoxic plasma levels in patients with cancer,[38] has shown clinical effectiveness in those with NSCLC receiving platinum doublet chemotherapy,[12] and allows for a feasible infusion time. Weight will be measured at baseline to determine the treatment dose and will be taken at each infusion; the dose will be adjusted if the participant's weight changes by 5 kg or more. Infusions will begin with a 15 g dose for the first session and will increase in steps to rapidly reach a dose of 1g/kg (according to baseline weight). After the 15g dose, the second treatment will be 50g, and the remaining treatments will be 1g/kg. For example, a 75 kg adult would first receive a 15 g dose, a second 50 g dose, and then a 75 g dose, which they would receive for the remainder of the treatment period. The minimum maintenance dose will be 50 g and the maximum dose will not exceed 100 g. Each treatment length will not exceed 2 hours 30 minutes. The standard infusion rate will be at least 0.5g/min with the option of increasing up to 0.67g/min for infusions greater than 75g in order to maintain the 150-minute time limit. If the participant cannot tolerate 0.5g/min, their treatment will be discontinued and they will be withdrawn from the study. Doses will be rounded up to the nearest 5g increment. Equivalent sized bags will be prepared to achieve slightly hypertonic osmolarity with respect to ascorbic acid or the saline-based placebo. Should a treatment fall on a public holiday (i.e., when the CHI is closed), treatment will be scheduled on the next available business day.

If an infusion does not take place within 1 day of the scheduled date, it will be considered missed.

4.7.1 IV Bag Preparation

The ascorbic acid and placebo infusions will be compounded at The Centre for Health Innovation by qualified personnel who otherwise are uninvolved with the study. IVC will be compounded in sterile water, whereas placebo infusions will be 0.9% sodium chloride solutions (normal saline, NS). Study labels will comply with all Health Canada regulations and contain the drug identification number for IVC, brand name, expiry date, storage conditions and lot number alongside a unique study identifier. An additional label will be added to each bag with a statement indicating that it is an investigational product to be used only by a qualified investigator, the trial's sponsor name and address and protocol code. These labels will be affixed to each bag completely obscuring the original label contents, if any.

4.7.2 Discontinuation of Chemotherapy

Should a participant's chemotherapy be terminated prematurely, they will continue study treatments per the protocol, provided they do not meet any criteria listed in section 3.6.

Creatinine will continue to be collected at the CHI and analyzed at Dynacare each 3 weeks in these participants.

4.8 Randomization, Blinding and Placebo Control

Patients will be web-randomized in blocks of 2 and 4 in a 1:1 ratio of treatment to placebo. Stratification will occur for stage IIIB and IV patients; however, there are no specific recruitment targets per strata. Participants, investigators, researchers, and other healthcare providers within the participant's circle of care will be blinded to treatment allocation. The exception will be delegated study personnel responsible for preparation (i.e., compounding) of the investigational product and investigational product management. This team will function as the study's "pharmacy" and will be led by Dr. Flower. Any personnel delegated the tasks of investigational product compounding, dispensing, or general product management will not be delegated any other study tasks and will not have any contact with participants. Un-blinding may only occur for safety purposes. The randomization database will be created and maintained by the Ottawa Methods Centre. Infusion bags will be prepared at the Centre for Health Innovation and will be identical in appearance except for study ID, which will allow the research team to administer the correct bag, and lot number, which will allow the person compounding to distinguish between IVC and placebo. Bags will be opaque and IV lines will be tinted or covered to mask any differences in colour. Normal saline infusions will run at equivalent rates to IVC infusions that will be based on baseline weight (see table 1).

4.9 Study Setting

The study will take place in Ottawa and involve teams at The Ottawa Hospital Cancer Centre and the Patterson Institute for Integrative Oncology Research. Infusions will take place at The Centre for Health Innovation (CHI). Consent, chemotherapy-related AE recording and usual care will be handled by TOHCC. Placebo and verum infusions will be given at the CHI by an ND or a registered nurse; study-related outcomes will be collected at both primary locations; the qualified investigator will oversee trial conduct and communicate regularly with the Co-Principal Investigator, research staff, and medical oncology team. While all study activities will take place at TOHCC and the Patterson Institute, patients might receive their standard-of-care chemotherapy infusions at off-site locations (e.g., Irving Greenberg Family Cancer Centre).

5 Sample Size Determination and Power Calculation

Based on previous research, the average FACT-L trial outcome index (TOI) scores in patients with advanced non-small lung cancer is approximately 55.5 ± 14.9 on a scale of 0-84.[39] A sample size of 90 patients (45 control, 45 treatment) is required to note a 9 point (roughly 11%) change in this quality of life measure. This change represents a clinically relevant and meaningful

outcome for this highly debilitated patient population.[40-42] This calculation is based on applying 80% power with an alpha of 0.05. The TOI was chosen for the power calculation over FACT-G and FACT-T as it has been reported as the most clinically relevant QOL indicator in lung cancer trials.[40]

6 Data Management, Analysis, and Monitoring

6.1 Data Management

All outcomes – including those that are patient-reported, clinician-derived and coordinator facilitated – will be completed using electronic case report forms (eCRFs) developed by the Ottawa Methods Centre. Research coordinators at both the CHI and TOHCC will be able to access these eCRFs and upload participant-related data directly. Participants are able, and encouraged, to input their own questionnaire outcomes on-site using tablets or smart phones. Any paper source documents will be stored in locked cabinets accessible only by delegated study staff. Electronic databases will be stored on The Ottawa Hospital's secure server and will be password protected.

6.2 Statistical Methods

Continuous variables (e.g., FACT, ESAS scores) will be analyzed using unadjusted t tests. Dichotomous outcomes (e.g., incidence of adverse events, discontinuation of chemotherapy) will be analyzed using the chi-squared test or Fisher's exact test as appropriate. Tumour progression and survival outcomes will be graphically depicted with Kaplan-Meier curves and compared using the log-rank test. All testing will be done at the 0.05 level of significance.

6.3 Data Monitoring and Stopping Rule

External oversight for this trial will be provided by an independent Data Safety and Monitoring Board (DSMB). The primary responsibility of the DSMB is to protect the safety and welfare of participants who take part in this clinical trial and to ensure the integrity of the clinical trial. The DSMB will meet either in-person or remotely to discuss matters related to the safety of study participants, validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol, and data completeness.

The DSMB will conduct their first review once 6 participants have been enrolled and completed at least half of their treatments. Continued review will occur at least annually until the last participant completes all treatments. The DSMB may review data at other times at their discretion. Based on review of the safety data, the DSMB may recommend continuation of the study without modification(s), study interruption, study termination, or modification of the trial,

where applicable. Further information regarding the DSMB review process is provided in the Study DSMB Charter.

6.3.1 Stopping Rule

This study will contain a stopping rule to ensure feasibility. Feasibility will be assessed at one year. The following conditions must be met:

- Enrollment and randomization of 10 patients
- Retention rate of at least 60%
- When eligible, compliance of at least 50% with the study intervention
- Serum ascorbate level of at least 15 mM in 80% of participants

If any of the above conditions are not met after the first year of recruitment, the study will be deemed infeasible.

7 Adverse Events: Definitions and Reporting Requirements

7.1 Definitions

Adverse Event: According to the principles of ICH GCP, an Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, a natural health product, or for whom a treatment or intervention is provided, and which does not necessarily have to have a causal relationship with this treatment.

Serious Adverse Event: A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. As such, it does not refer to an event which hypothetically might have caused death if it were more severe.

Adverse Drug Reaction: An adverse drug reaction is defined as a noxious and unintended response to a medicinal product related to any dose. This means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Unexpected Adverse Drug Reaction: Adverse drug reactions in which the nature or severity is not consistent with the applicable product information (i.e., the product monograph).

7.2 Expected Adverse Events

According to reports in the literature and clinical experience, the expected adverse events associated with each component of the intervention are listed below.

In accordance with the literature and clinical experience, the following adverse events are expected among patients receiving IV ascorbic acid:

Very common (≥10%): dry mouth, nausea, transient hypertension, hyponatremia

Common (Between 1 and 10%): increased thirst, increased urination, diarrhea, fatigue, weakness, headache, light-headedness, dizziness, injection site discomfort, phlebitis, arthralgia/myalgia, chills, dysgeusia, hypokalemia, hypomagnesemia, hypocalcemia, hypernatremia, hypotension, neuropathy, hemolysis, loss of appetite

Uncommon (Between 0.1 and 1%): abdominal cramping, facial flushing, vomiting, kidney stones, lower urinary tract symptoms, insomnia, abnormal urine colour, hyperglycemia, fever, swelling of feet or lower legs, sweating, ascites, allergic reaction, acute oxalate nephropathy, renal failure in those with a pre-existing renal condition.

Very rare (<0.01%): atrial fibrillation (one report)

Expected serious adverse events include acute oxalate nephropathy, renal failure, and atrial fibrillation.

In addition, as patients in this study are lung cancer patients undergoing chemotherapy, they may experience events that would be considered unexpected in relationship to the study drug (IVC) but expected for this population. Chemotherapy side effects from platinum doublet chemotherapy are well described and can generally be divided into immediate, acute, short-term, and long-term side effects.

Immediate: infusion reactions

Acute: nausea and vomiting

Short term: fatigue, tinnitus, nausea and vomiting, diarrhea or constipation, neutropenia and/or febrile neutropenia, anemia or thrombocytopenia, anemia-induced infections, anemia-induced dyspnea/bleeding

Long-term: cytopenia, peripheral neuropathy, renal impairment, second malignancy.

Expected serious adverse events include febrile neutropenia, cytopenia, renal impairment, and second malignancies.

7.3 Collection and Reporting

Adverse events will be collected for safety using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Collection will start after the participant has started receiving IV infusions and will continue until treatment stops. Participants in both arms will be asked about adverse events at each visit with a member of the research team, including all IV infusions and standard of care follow-ups. Upon completion of treatment, or in the event a participant is removed from the study (i.e., withdraws or is deemed a screen fail), ongoing AEs will be followed for an additional 4 weeks. All serious adverse events will be followed until they are resolved.

SAEs will be reported to the REBs according to local requirements. All other AEs will be reported to the REBs in an annual renewal report. The frequency and nature of SAEs will be documented and reported to the DSMB.

All serious unexpected adverse drug reactions will be reported to the TPD. These adverse events are subject to expedited reporting; therefore, if an event is determined to be serious, and related or possibly related to the intervention, and not expected as stated in the product monograph, protocol, or consent form, the trial coordinator will notify Health Canada as soon as possible but no later than 7 calendar days after becoming aware of the event for fatal or life-threatening events, and no later than 15 days after becoming aware for non-fatal/life threatening events.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home that does not require inpatient hospitalization or other severe adverse events that do not meet the criteria for being serious.

8 Privacy and Confidentiality

Patient personal health information (PHI) will be kept confidential unless release is required by law. Representatives of the OHSN-REB, Ottawa Hospital Research Institute, CCNM REB as well as the TPD may review original medical records under the supervision of Dr. Seely's staff for audit purposes.

Patients enrolled in the study will not be identified in any publications or presentations resulting from this study unless permission is given by the patient. All databases will be password protected on a secure server. This data and relevant source documents will be kept for a period of 15 years as required by Health Canada. Databases will be erased at the end of this retention period.

9 Dissemination and Knowledge Transfer

Given the important and innovative nature of this trial, widespread dissemination of the research will be made. Dissemination will include scientific presentations to complementary, integrative, and traditional medical conferences within Canada and internationally. Presentations will be accompanied by published abstracts. The principal mechanism for knowledge transfer will be publication and will include the use of social media as well as press. We will target the most reputable clinical journal for publication due to the potential impact of this investigation.

10 Relevance and Impact

To date, no double-blind, randomized, placebo-controlled trial has investigated the effect of IV ascorbic acid in conjunction with chemotherapy in patients with lung cancer. Should this study demonstrate a positive impact from IV ascorbic acid, it could lead to more definitive research and have a substantial clinical impact.

With the public usage of IV ascorbic acid currently taking place, the belief in this therapy, and the promise of some of the research and its inconclusive nature, further well controlled clinical research on this therapy is essential. The potential exists to influence standard of care, be supported financially by health agencies, and lead to improved cancer therapy outcomes.

A positive trial paves the way for future research and a possible paradigm shift in the view and research for this therapy. A negative trial will help prevent patients from paying thousands of dollars out of pocket for an ineffective therapy. Either way, this study will help to clarify the role of IVC as it relates to advanced lung cancer and potentially other cancer types as well.

This initiative is timely and brings together the required expertise and experience to conduct a rigorous phase II randomized clinical trial in a population of cancer patients that could benefit greatly. If no benefit is found from this trial, then this is equally valuable as it may save thousands of patients from needless expenditure and lost time.

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