Thomas Jefferson University

THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

A PILOT STUDY OF INTRAVENOUS ASCORBIC ACID AND FIRINOX IN THE TREATMENT OF ADVANCED PANCREATIC CANCER

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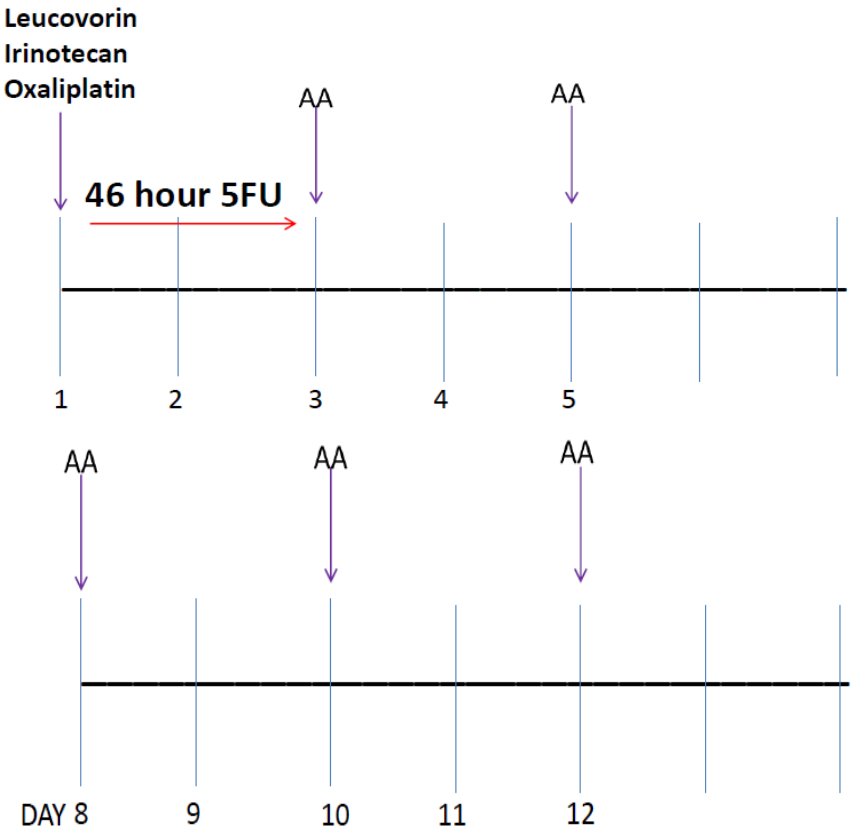
List of Abbreviations

5FU	5 Flourouracil
AA	Ascorbic acid
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
BSA	Body Surface Area
CHF	Congestive Heart Failure
CIPN	Chemotherapy Induced Peripheral Neuropathy
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CrCL	Creatinine Clearance
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
EKG	Electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FIRINOX	Combination of infusional 5 fluorouracil, oxaliplatin and irinotecan
FOLFIRINOX	Combination of folinic acid, bolus and infusional 5 fluorouracil, oxaliplatin and irinotecan
G6PD	Glucose 6 Phosphatase deficiency
GCSF	Granulocyte Colony Stimulating Factor GI: Gastrointestinal
IV	Intravenous
M^2	Meter Squared
MG	MilliGrams
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PI	Principal Investigator
PRO	Patient Reported Outcomes
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplatin Time
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SC	Sub-Cutaneous
SGA	Subjective Global Assessment
TITE-CRM	Time to event continual reassessment method
ULN	Upper Limit of Normal
WBC	White Blood Cells

Study Summary

Title	A Pilot Study of Intravenous Ascorbic Acid and FIRINOX in the Treatment of Advanced Pancreatic Cancer
Short Title	IV Ascorbic acid + FIRINOX in pancreatic cancer.
Phase	Pilot
Methodology/Study Design	Time-to-event continual reassessment method, open label, single arm
Study Duration	1 year
Study Center(s)	Thomas Jefferson University
Objectives	1) Safety of Ascorbic acid + FIRINOX. 2) Feasibility of collecting QOL questionnaires in advanced pancreatic cancer.
Number of Subjects	8
Diagnosis and Main Inclusion Criteria	• Age 18-75 • Histological diagnosis of adenocarcinoma of the pancreas Stage IV or recurrent pancreatic cancer • Locally advanced unresectable pancreatic cancer • ECOG 0-1 • First line treatment (Neo-adjuvant or adjuvant chemotherapy or chemoradiation allowed) • Adequate hematologic and chemistry parameters • No clinical ascites (mild ascites on scans permissible) • No known CHF, ventricular arrhythmias, cirrhosis, uncontrolled diabetes • No preexisting peripheral neuropathy
Study Therapy, Dose, Route, Regimen	Ascorbic acid 100 grams IV 2-3 times a week
Duration of administration and follow-up	Till progression (RECIST 1.1), intolerance, withdrawal, noncompliance or death Follow up 30 days
Reference therapy	Modified FOLFIRINOX

Statistical Methodology	The study will follow a Phase I design for toxicities called the time-to-event continual reassessment method. We will enroll 8 patients and monitor toxicities for 28 days. The expected accrual rate is one patient a month. The first patient will be started at the highest dose. Change in quality of life over three measurement times will be modeled using mixed effects linear regression to account for correlation among repeated measurements from the same subjects.
Schema	 Ascorbic acid infusions can be adjusted by up to 72 hours to account for weekends, holidays, clinic schedules and patient convenience. Treatment delays more than 72 hours may be allowed after discussion with PI. Example schema:

Monday	D1 - FIRINOX	D8 - Ascorbic acid
Tuesday	D2 - 5FU	D9
Wednesday	D3 - 5FU disconnect + Ascorbic acid	D10 - Ascorbic acid
Thursday	D4	D11
Friday	D5 Ascorbic acid	D12 - Ascorbic acid
Saturday	D6	D13
Sunday	D7	D14

Brief Rationale:
Combination of infusional 5 fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) is the most active regimen in the treatment of metastatic pancreatic cancer. Its widespread use is limited by a higher number of side effects compared to gemcitabine.(Conroy et al., 2011) However, FOLFIRINOX significantly improves Quality of Life (QOL) compared to gemcitabine in spite of the reported higher side effects.(Gourgou-Bourgade et al., 2013) High dose parenteral ascorbic acid has been shown to enhance chemosensitivity and decrease toxicity associated with chemotherapy in ovarian cancer patients in a small randomized trial.(Ma et al., 2014) Newer agents are unlikely to be added to FOLFIRINOX due to perceived toxicity and lack of a clear path to Food and Drug Administration (FDA) approval. FOLFIRINOX regimen is routinely modified by removing the bolus 5FU to decrease risk of neutropenia and other side effects. Folinic acid which modulates the action of bolus 5FU is not needed when the bolus 5FU is eliminated. If FIRINOX regimen (without the bolus 5FU and leucovorin, also referred to as modified FOLFIRINOX) can be made more tolerable, it may have a greater impact on metastatic pancreatic cancer patients, than trying to improve survival marginally with less active regimens.

Dose Limiting Toxicity (DLT):

- Any Grade 5 event attributable to the regimen
- Any Grade 4 non-hematological toxicity that is attributable to regimen
- Nausea, vomiting or diarrhea ≥ Grade 3 that persists for greater than 72 hours despite optimal antiemetic or anti-diarrheal therapy and IV hydration
- Any Grade 3 or higher non-hematological toxicity that is study drug related that results in delay in FIRINOX chemotherapy by greater than 2 weeks

QOL Management:

- Eastern Cooperative Oncology Group (ECOG) Performance Status every 2 weeks (Appendix 2)
- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) 30 every 2 weeks (appendix 3)
- EORTC Chemotherapy-Induced Peripheral Neuropathy (CIPN) 20 every month (appendix 4)
- Oxaliplatin neuropathy scale every month (appendix 5)
- Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale every 2 months (appendix 6)
- Subjective Global Assessment (SGA) every 2 months (appendix 7)

1.0 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background and Rationale

Pancreatic Cancer

There were an estimated 48,960 new cases of pancreatic cancer and 40,560 estimated deaths from pancreatic cancer in the United States in 2015.(Siegel, Miller, & Jemal, 2015) 5 years survival of newly diagnosed pancreatic cancer patients is only 6 to 7%.(Siegel et al., 2015). Pancreas cancer is the 4th leading cause of cancer death and is expected to be the 2nd leading cause of cancer death by 2020.(Rahib et al., 2014) Surgery is currently the only effective curative treatment; however only 10-20% of patients diagnosed with pancreas cancer can actually have a curative resection.(Conlon, Klimstra, & Brennan, 1996; Shaib, Davila, Naumann, & El-Serag, 2007) Of the patients who undergo resection, tumor recurrence occurs in over 80 % of patients over time. Therefore 5 year survival of resected pancreatic cancer is only about 20 %. (Mayo et al., 2012; Winter et al., 2006) Patients who present with metastatic pancreatic cancer have a dismal survival with a 1 year survival of only 20% and have a median survival of about 6 months with gemcitabine. (Burris et al., 1997)

Treatment of Pancreatic Cancer:

Adjuvant therapy with gemcitabine improves disease free survival, overall survival and doubles 5 year survival compared to observation alone. (Oettle et al., 2013) The role of radiation after surgery is controversial with some studies showing a benefit and others showing no benefit and potential harm. (Kalser & Ellenberg, 1985; Klinkenbijl et al., 1999; Neoptolemos et al., 2004) In the United States, adjuvant gemcitabine and chemoradiation is commonly used. For patients with unresectable disease, treatment is palliative and chemotherapy is recommended to prolong survival and improve quality of life. (Yip, Karapetis, Strickland, Steer, & Goldstein, 2006) Gemcitabine was initially approved based on improvement in clinical benefit rate, a composite of pain control, weight gain and survival. (Burris et al., 1997) Combining gemcitabine with other cytotoxic chemotherapy agents has been largely unsuccessful until recently. The National Cancer Institute Canada PA3 trial demonstrated that the combination of gemcitabine with erotinib resulted in a statistically significant improvement in overall survival when compared to gemcitabine and placebo (hazard ration 0.81, p=0.025). (Moore et al., 2007) Median survival in the gemcitabine plus erlotinib arm was 6.4 months compared to 5.9 months in the gemcitabine plus placebo arm questioning whether this improvement in survival is clinically significant. More recently multi- agent chemotherapy with FOLFIRINOX and gemcitabine + nab-paclitaxel has shown encouraging results. (Conroy et al., 2011; Von Hoff et al., 2011)

A recent phase III clinical trial of nab-paclitaxel in combination with gemcitabine in treatment-naïve patients with metastatic pancreatic cancer demonstrated a statistically significant improvement in overall survival compared to patients receiving gemcitabine

alone [(median of 8.5 vs. 6.7 months) (HR 0.72, P=0.000015)]. (Von Hoff et al., 2011) In the MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) study, nab-paclitaxel plus gemcitabine demonstrated a 59% increase in one-year survival (35% vs. 22%, p=0.0002) and demonstrated double the rate of survival at two years (9% vs. 4%, p=0.02) as compared to gemcitabine alone. Nab-paclitaxel plus gemcitabine also demonstrated a statistically significant improvement in key secondary endpoints compared to gemcitabine alone, including a 31% reduction in the risk of progression or death with a median progression-free survival (PFS) of 5.5 vs. 3.7 months (HR 0.69, P=0.000024) and an overall response rate (ORR) of 23% compared to 7% (response rate ratio of 3.19, p=1.1 x 10-10). The most common grade ≥ 3 treatment-related adverse events in the study for nab-paclitaxel plus gemcitabine vs. gemcitabine alone were neutropenia (38% vs. 27%), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). In the nab-paclitaxel plus gemcitabine arm, the median time to neuropathy improvement was 29 days. There was no difference in serious life threatening toxicity (4% in each arm).

FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks) was compared to standard gemcitabine monotherapy in 342 patients with an ECOG PS=0 or 1 in the PRODIGE/ACCORD French trial.(Conroy et al., 2011) The primary endpoint was overall survival (OS), with a median OS of 11.1 months in the FOLFIRINOX group vs 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival (PFS) was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate (RR) was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001). Despite more adverse events in the FOLFIRINOX group, including a neutropenia, febrile neutropenia, diarrhea, neuropathy and LFT abnormalities, at 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001). There was also improvement in global health status in the FOLFIRINOX arm. (Conroy et al., 2011; Gourgou-Bourgade et al., 2013) FOLFIRINOX regimen is routinely modified by removing the bolus 5FU or decrease the irinotecan dose to decrease the risk of side effects and make it more tolerable. (Mahaseth et al., 2013; Chllamma et al.,2016; Gunturu et al.,2013) Folinic acid which modulates the action of bolus 5FU is not needed when the bolus 5FU is eliminated.

FOLFIRINOX has been adopted as a standard of care for newly diagnosed metastatic or unresectable pancreatic cancer patients with a good performance status. Patients treated with FOLFIRINOX have a 9% incidence of grade 3 or 4 sensory neuropathy and many patients discontinue treatment due to neuropathy. (Conroy et al., 2011) If FOLFIRINOX can be made more tolerable with lesser side effects, more patients can get treatment shown to have the best efficacy data in metastatic pancreatic cancer. Pancreatic cancer has a high symptom burden with short survival and the goals of

treatment are palliative.(Gourgou-Bourgade et al., 2013) QOL is as important as prolonging survival in incurable patients and ways to improve QOL are needed.

EORTC QLQ C 30 is a validated tool to objectively measure quality of life in cancer patients.(Aaronson et al., 1993) It was used in the pivotal trial of FOLFIRINOX to prospectively collect longitudional QOL as a secondary endpoint.(Conroy et al., 2011; Gourgou-Bourgade et al., 2013) QLQ CIPN 20 is a validated tool to objectively measure peripheral neuropathy in patients.(Postma et al., 2005) A scale to specifically measure oxalipalatin induced neuropathy has been developed.(Leonard et al., 2005) Since oxaliplatin causes both acute neurosensory complex which develops soon after infusion and also cumulative sensory neuropathy. The acute neuropathy manifests as discomfort swallowing cold foods, sensitivity to touch cold items and paresthesisas of the perioral region. Symptoms usually resolve in 1-4 days. Fatigue is the most common complaint in patients undergoing chemotherapy. (Yeo et al., 2012) FACIT-F scale is a very brief, but reliable and valid measure of fatigue in cancer patients.(Yellen, Cella, Webster, Blendowski, & Kaplan, 1997) Pancreatic cancer patients with a higher FACIT-F score had a lower median overall survival in a randomized, placebo controlled phase 2 study collecting PRO.(Robinson et al., 2008) Pancreatic cancer patients frequently also manifest with cachexia and weight loss. The patient generated subjective global assessment questionnaires can be used as a nutrition assessment tool that identifies malnutrition in ambulatory oncology patients. (Isenring, Bauer, & Capra, 2003) Feasibility of collecting QOL and PRO data will enable design of future clinical trials.

1.2 Study Therapy

Intravenous, high dose ascorbic acid is a widely used alternative cancer treatment, although its use as such has not been appropriately tested in randomized controlled studies. Linus Pauling reported prolonged survival in terminal cancer patients in an open labelled study using oral and intravenous ascorbic acid.(Cameron & Campbell, 1974; Cameron & Pauling, 1976, 1978) Ascorbic acid as a cancer therapy was largely discarded when two randomized trials of oral ascorbic acid therapy done at the Mayo Clinic failed to demonstrate therapeutic benefit. (Creagan et al., 1979; Moertel et al., 1985) However, pharmacokinetic modelling indicates that intravenous administration of Ascorbic acid produces a 25-fold or greater plasma concentration than the same dose given orally.(Padayatty et al., 2004; Verrax & Calderon, 2009) Chen and associates have reported that ascorbic acid levels achievable in vivo by intravenous infusion are selectively cytotoxic in vitro to various cancer cell lines but not to normal cells by a mechanism involving formation of hydrogen peroxide.(Chen et al., 2005; Du et al., 2010) This mechanism is dependent on pro-oxidant actions, as a consequence of ascorbic acid concentrations achieved only by intravenous administration. Ascorbic acid is generally a chemically reducing agent (anti-oxidant), or electron donor. However, at pharmacologic concentrations, ascorbic acid electron donation sets in motion a series of chemical reactions whose end result is formation of hydrogen peroxide and subsequent pro-oxidant compounds, with selective toxicity to cancer but not normal cells. Thus, while ascorbic acid action is always as an electron donor, its actions at pharmacologic concentrations produce pro-oxidant consequences. The mechanism of action of Ascorbic acid as a prodrug for hydrogen peroxide formation in the extravascular space has been confirmed by the laboratory of study consultant

Mark Levine, M.D., Ph.D. (Chen et al., 2007; Sestili, Brandi, Brambilla, Cattabeni, & Cantoni, 1996; Verrax & Calderon, 2009) This action of IV Ascorbic acid is consistent with a growing literature that reactive oxygen species play an important role in the mechanism of action of proven cancer treatments and that impaired oxygen-reduction balance in cancer cells might cause induced reactive oxygen species to selectively kill cancer cell.(Chen et al., 2007; Du et al., 2010) Since FDA does not approve vitamins, ascorbic acid has not been approved by the FDA although it is widely used to treat different medical conditions including cancer. High dose intravenous ascorbic acid therefore should be given only in the context of clinical trial to evaluate its true efficacy. (Parrow, Leshin, & Levine, 2013; Welsh et al., 2013)

1.3 Preclinical Data

Studies on tumor xenographs in mice confirming ascorbic acid as a prooxidant showed decreased growth of three aggressive tumor types: Pancreatic, glioblastoma, and ovarian (Chen, 2008). To test this action in vivo, the investigators bypassed normal oral tight control with parenteral ascorbic acid administration. Real-time microdialysis sampling in mice bearing glioblastoma xenografts showed that a single pharmacologic dose of ascorbic acid produced sustained ascorbic acid radical and hydrogen peroxide formation selectively within interstitial fluids of tumors but not in blood. Moreover, a regimen of daily pharmacologic ascorbic acid treatment significantly decreased growth rates of ovarian ($P < 0.005$), pancreatic ($P < 0.05$), and glioblastoma ($P < 0.001$) tumors established in mice. Also in this study, similar pharmacologic concentrations were readily achieved in humans given ascorbic acid intravenously. These data suggest that ascorbic acid as a prodrug may have benefits for some cancers. Overall, recent in vitro biological evidence, limited human case data, clinical pharmacokinetic data, and recent in vivo data confer biological plausibility to the notion that ascorbic acid could affect cancer biology and that there is reason to explore the therapeutic concept. (Du et al., 2010; Welsh et al., 2013) More research data is needed to guide the current wide use of high dose intravenous ascorbic acid**.** (Hoffer et al., 2015; Ohno, Ohno, Suzuki, Soma, & Inoue, 2009)

1.4 Clinical Data to Date

Thousands of patients are treated every year with intravenous ascorbic acid for infection, cancer and fatigue by integrative medicine practitioners. A large survey showed that most practitioners report no serious adverse event even at high doses. Side effects are minor and include lethargy, fatigue, phlebitis and dizziness. (Padayatty et al., 2010)

A phase 1 dose escalation clinical trial in 24 advanced cancer patients showed that Maximum Tolerated Dose (MTD) was not reached at 1.5/kg of intravenous ascorbic acid as single agent. (Hoffer et al., 2008) The only grade 2 Adverse Events (AE) noted was dizziness, flushing, vomiting and headache. No abnormal hematologic or biochemical parameters were noted. Unfortunately no objective tumor responses were noted either with single agent intravenous ascorbic acid. (Hoffer et al., 2008) A dose of 1.5g/Kg was the recommended phase 2 dose (RP2D) for future studies. Another phase 1 study using intravenous ascorbic acid for 4 days a week also did not reach MTD and a dose of 70-80g/m^2. (Stephenson, Levin, Spector, & Lis, 2013) A phase 1

study with concurrent gemcitabine showed that treatment with intravenous ascorbic acid 15-125 grams twice weekly was well tolerated.(Welsh et al., 2013) We completed a phase 1 study of intravenous ascorbic acid in combination with gemcitabine and erlotinib and the results are presented below.(Monti et al., 2012)

Data from Phase 1 Intravenous Ascorbic Acid in Combination with Gemcitabine and Erlotinib in the Treatment of Metastatic Pancreatic Cancer . TJU IRB# 09D.99:

We attempted to determine the initial safety and efficacy of high dose intravenous ascorbic acid in combination with gemcitabine and erlotinib chemotherapy in patients with metastatic pancreatic cancer. A phase 1 study of Intravenous (IV) ascorbic acid was completed at Thomas Jefferson University. Fourteen subjects (4 male and 10 female) with pancreatic cancer metastatic to the liver and other organs were recruited to receive an 8 week cycle of intravenous AA given three times per week in addition to standard treatment with gemcitabine (1000mg/m^2/wk) and daily erlotinib, using a standard 3+3 dose escalating design (50grams, 75grams, and 100grams). Data were obtained regarding laboratory values and adverse events throughout the treatment period. In addition, subjects received either Computerized Tomography (CT) of the chest, abdomen, and pelvis, or a whole body Positron Emission Tomography PET-CT scans to evaluate for response to treatment using Response Evaluation Criteria In Solid Tumors (RECIST) criteria.

Patient Cohort:

Overall, 14 patients were recruited with 4 males and 10 females and a mean age of 64.4 (±10.0) (range 47-81). All patients had pancreatic adenocarcinoma that was either metastatic or locally advanced. Nine patients received the full cycle of ascorbic acid plus gemicitabine/erlotinib treatments. The full cycle was defined as at least 24 (±6) treatments for 8 (±1) weeks. Five patients did not complete the study. Two subjects (003 and 007) chose not to continue. Three subjects died from progression of disease (subjects 009 after only 5 weeks of treatment, 011 after only 3 weeks of treatment, and 014 after only 1 week of treatment) and could not be evaluated using imaging. The other nine subjects were included in the CT evaluation for response to therapy.

Safety Evaluation:

The most common reported adverse event was mild light headedness when patients are receiving the intravenous ascorbic acid usually resolving with eating and drinking. For the total cohort of 14 patients, there were 23 total adverse events with 8 being serious adverse events. The adverse events are shown in Table 2. All of these adverse events were most likely attributable to progression of disease or concomitant treatment with gemcitabine/erlotinib. One male subject was hospitalized with low hemoglobin due to an internal bleed and then was subsequently placed on hospice care. Two subjects were found to have a pulmonary embolism most likely related to the underlying pancreatic cancer that has a reported rate of Pulmonary Embolism (PE) between 20-50%. Three subjects died from progression of the underlying cancer. One patient was hospitalized twice, once for anemia symptoms and once for a UTI Urinary Tract Infection (UTI) which both resolved. A male subject was hospitalized with abdominal pain and ileus which he actually had at the study onset, and he received Total Parental

Nutrition (TPN) and Nasogastric tube feeds, but was finally put on hospice before dying of the underlying cancer. None of these subjects received the full treatment with the IV ascorbic acid. None of these adverse events appear to be specifically related to the Ascorbic acid treatment since each of these events is frequently observed in the normal progression of pancreatic cancer patients and/or gemcitibine and erlotinib treatment.

Response to Treatment Based on CT Results:

With regard to efficacy, 9 patients underwent pre and post treatment CT scans. Scans were evaluated for the change in size of the primary tumor as well as by using RECIST criteria (see Table 3). The results showed that all patients had a reduction in size of the primary tumor (with one patient having no change in size). By RECIST criteria, 6 patients had stable disease and 3 patients had progressive disease. However, two patients in the highest dose range (100g per infusion) actually had a reduction in size of the primary tumor and a reduction in the metastatic sites. However, the reduction in the target lesion size was not sufficient to be reported as a partial response by RECIST 1.0 criteria which require a 30% reduction in size in the target lesions.

The three dosage levels were generally well tolerated with similar AE profiles for each with no AE's other than what might be expected for progression of pancreatic cancer and/or treatment with gemcitabine and erlotinib. Thus, there were no dose-limiting toxicities and the target dose of 100 grams was not associated with increased adverse events.

Table 1: Patient Demographics and Disease Status

ID	Age/ Gender	Time Dx to Rx	Dx (in addition to pancreatic primary mass)*	Dose Level (g/infusion)	Doses	Weeks
001	60 M	3 wks	Liver/lung/media	50	24	8
002	75 F	5 wks	Liver/retroper	50	24	8
003	81 F	5 wks	Locally adv	50	3	1
004	64 F	4 wks	Liver	50	18	7
005	69 M	6 mon	Locally adv	75	23	8
006	66 F	2 wks	Media/retroper	75	22	8
007	47 F	6 wks	Liver/peritoneal	75	3	1
008	75 F	3 wks	Liver	75	21	7
009	51 M	3 mon	Liver/peritoneal	75	14	5
010	48 F	3 wks	Liver	100	21	8
011	67 F	4 wks	Liver/peritoneal	100	9	3
012	67 F	4 mon	Locally adv/bone	100	24	8
013	66 F	3 wks	Liver	100	24	8
014	65 M	4 mon	Liver/peritoneal	100	3	1

Bone=bone metastases, Liver=liver metastases, Locally adv=locally advanced spread of cancer, Lung=lung metastases, Media=mediastinal metastases Peritoneal=peritoneal metastases, Retroper=retroperitoneal nodes or metastases

Table 2. Adverse Event Chart for all 14 patients.

Adverse Event	Number of Events
Low Platelets	
Grade 1	6
Grade 2	2
Low Hemoglobin	
Grade 2	1
Grade 3	2
Low ANC	
Grade 3	1
Elevated Glucose	
Grade 2	1
Gastrointestinal	
Ileus (Grade 3)	1
Discomfort (Grade 2)	1
Ascites (Grade 2)	1
Infection	
Conjunctival (Grade 2)	1
UTI (Grade 3)	1
Pulmonary Emboli	
Grade 4	2
Death	
Grade 5	3

Table 3. Response to ascorbic acid plus gemcitabine based on CT findings in patients with scans pre and post the 8 week ascorbic acid treatment cycle plus gemcitabine/erlotnib.

Patient (Dose)	Pancreatic Mass Pre (mm)	Pancreatic Mass Post (mm)	% Change Primary Mass	Non-Target Lesions	RECIST Criteria Response
001 (50g)	32 x 20	28 x 22	-13%	Progressed	PD
002 (50g)	31 x 18	18 x 16	-42%	Stable	SD
004 (50g)	43 x 39	33 x 39	-23%	Stable	SD
005 (75g)	43 x 19	38 x 21	-12%	Stable	SD
006 (75g)	92 x 42	82 x 36	-11%	Progressed	PD
008 (75g)	41 x 38	41 x 38	0%	Progressed	PD
010 (100g)	42 x 22	36 x 17	-14%	Improved	SD
012 (100g)	59 x 38	48 x 37	-19%	Stable	SD
013 (100g)	49 x 49	44 x 42	-10%	Improved	SD

These findings suggest that IV Ascorbic Acid (AA) is relatively safe in pancreatic cancer

patients receiving gemcitabine and erlotinib, which is consistent with previous studies on the safety of AA in cancer populations. The results also suggest the need for the further studies to assess the use of IV AA in patients with metastatic pancreatic cancer. As more effective chemotherapy backbones like FOLFIRINOX are now available, gemcitabine+erlotinib is no longer considered an acceptable first line regimen for fit patients.

A recent study of ascorbic acid in advanced ovarian cancer showed cytotoxic effects on cancer cells in vivo, synergizing with chemotherapy and decrease in tumors in a mouse xenograft model. (Ma et al., 2014) In a pilot study of 27 patients, patients were randomized to standard first line carboplatin and paclitaxel chemotherapy with or without ascorbic acid. Patient who received intravenous ascorbic acid had decreased frequency of grade 1 and 2 adverse events and longer time to disease progression. The study however was not powered to show a difference in survival. (Ma et al., 2014)

1.5 Dose Rationale and Risk/Benefits

Ascorbic acid has been shown to be well tolerated even when administered intravenously, and phase I human data from a group of 24 mixed cancer patients confirm it to be relatively safe and non-toxic, even at doses as high as 1.5 grams/Kg (Hoffer et al., 2008; Hoffer et al., 2015; Stephenson et al., 2013). This study reported only mild adverse effects associated with such doses of ascorbic acid. Two cases of acute oxalate nephropathy were reported in patients with pre- existing renal insufficiency given massive intravenous doses of vitamin; (Wong, Thomson, Bailey, McDiarmid, & Gardner, 1994) therefore, patients with renal insufficiency or renal failure, or who are undergoing dialysis, should not receive high doses of ascorbic acid. There are two reports of intravascular hemolysis in people infused with more than 50 g ascorbic acid and one that describes cases of hemolysis in persons who received at least 6 g of ascorbic acid as a single oral dose. All of the cases were in persons with the rare congenital metabolic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, which renders red blood cells susceptible to oxidative stress. (Riordan et al., 2004) G6PD status will be evaluated prior to start of therapy for all potential subjects. Our phase 1 study showed no Dose Limiting Toxicities (DLT) with 100 grams of ascorbic acid. (Monti et al., 2012) Since the toxicities of ascorbic acid and FIRINOX are not overlapping, we do not feel a dose escalation study is warranted. FIRINOX is standard chemotherapy and has reported the longest survival reported in a randomized trial in pancreatic cancer and therefore ascorbic acid is being added to this regimen to evaluate safety of the combination. As part of this study, patients will receive a modified FOLFIRINOX called FIRINOX as they will not be receiving the folinic acid (FOL).

<u>Special Risk Factors:</u>

Due to the frequency of the study regimen in combination with disease progression and standard treatment patients may experience fatigue and psychological distress about their diagnosis and prognosis which will be captured in QOL questionnaires.

<u>Risks of venous cannulation or Port access for ascorbic acid infusion:</u>

Venous cannulation and port accessing are routine clinical procedures that carry minimal risks when performed by trained personnel. It is possible that bruising/bleeding

could occur in some subjects. There is a risk of phlebitis or infection which is very low.

Teratogenic Effects: Pregnancy Category C:
Animal reproduction studies have not been conducted with ascorbic acid injection. It is not known whether ascorbic acid injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, ascorbic acid injections should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus and therefore pregnant women are excluded and women of child bearing age are encouraged to use contraception.

Nursing Mothers:
Ascorbic acid is excreted into human breast milk, but its effects on an infant are unknown. Thus, nursing women will be excluded from this study.

2.0 STUDY OBJECTIVES

Primary Objective:
The primary objective is to determine safety of intravenous ascorbic acid in combination with FIRINOX as defined by CTCAE version 4.03 in patients with advanced pancreatic cancer.

Secondary Objective:
The secondary objective is to test feasibility of collecting QOL, PRO data and correlative studies on patients with advanced pancreatic cancer.

3.0 STUDY DESIGN

3.1 General Design

This is a pilot study of 8 patients with pancreatic cancer. It is a single arm, non-randomized, open label study. Patients will continue on treatment till progression, death or withdrawal from the study. Patients who progress or are withdrawn from study will be followed for 30 days.

3.2 Primary Endpoint

Safety of the regimen as determined by CTCAE version 4.03.

3.3 Secondary Study Endpoint

Change in QOL as defined by EORTC QLQ C-30.

3.4 Exploratory End Points

Feasibility of collection of all QOL and PRO questionnaires.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Age 18-75 capable of giving informed consent
- Histological diagnosis of adenocarcinoma of the pancreas
- Stage IV or recurrent pancreatic cancer by imaging
- Locally advanced unresectable pancreatic cancer by NCCN criteria

- ECOG PS 0-1
- No prior treatment for metastatic disease (Prior neo-adjuvant or adjuvant chemotherapy, except FOLFIRINOX, chemoradiation or radiation allowed)
- White Blood Count >/= 3000, Platelets >/= 100,000
- Total bilirubin </= 1.5mg/dl, AST and ALT </= 5 X ULN Creatinine <1.5 mg/dL
- G6PD level of 5-14 units/g Hgb or within institutional standard parameters
- All subjects of child producing potential must agree to use contraception or avoidance of pregnancy measures while enrolled on study.

Exclusion Criteria

- Other pancreatic cancer histology. (islet cell, acinar, neuroendocrine tumors).
- Resectable pancreatic cancer
- Prior neoadjuvant FOLFIRINOX
- Pregnant or lactating females
- No clinical ascites (mild ascites on scans permissible)
- Central Nervous System (CNS) metastasis
- Known Congestive Heart Failure, significant ventricular arrhythmias, cirrhosis, grade 4/5 Chronic Kidney Disease, uncontrolled diabetes
- Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy.
- Peripheral neuropathy grade 2 or greater
- Any condition, psychiatric or otherwise, that would preclude informed consent, consistent follow-up or compliance with any aspect of the study (e.g., untreated schizophrenia or other significant cognitive impairment, etc.).

4.2 Gender/Minority Inclusion for Research

The ratio of men to women in pancreatic cancer is almost equal with slight male predominance. Participation of women and minorities is especially encouraged.

4.3 Subject Recruitment and Screening

8 patients, 18-75 years of age with a good performance status (ECOG 0 or 1) will be enrolled. Patients will be identified from the medical oncology practice at Thomas Jefferson University or referred from integrative medicine, surgery or other providers within and outside of Thomas Jefferson University. No advertisements are planned for the pilot study.

4.4 Early Withdrawal of Subjects

When and How to Withdraw Subjects:

Patients are withdrawn from the study of they have progression, intolerance, non-compliance, death or withdraw consent or continuing on the study is not in the patient's best interest as determined by the treating physician in collaboration with the principal investigator.

Data Collection and Follow-Up for Withdrawn Subjects:

Even though subjects may be withdrawn prematurely from the study, we will make all

efforts to collect at least survival data on all subjects every 6 months by phone call throughout the protocol defined follow-up period. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug.

If a subject withdraws consent or the treating investigator withdraws the patient from the study, every attempt will be made to obtain permission to record at least survival data every 6 months by phone call up to the protocol-described end of subject follow-up period using phone calls to next-of-kin if possible, certified letters or querying Social Security Administration's Death Index and obituaries.

5.0 STUDY DRUG/THERAPY

5.1 Ascorbic Acid

Ascorbic acid is a 6-carbon ketolactone structurally related to glucose and other hexoses. Its formal chemical structure is 3-oxo-L-gulofuranolactone, C6H8O6© 40.9%, H 4.6% O 54.5%), molecular weight 176.13.

Investigational Formulation and Supplier:
Ascorbic Acid Injection USP is ordered through the Thomas Jefferson University pharmacy and is provided free of charge to the study patients. It will be reconstituted and infused by the Myrna Brind Center. It is a clear, colorless to slightly yellow sterile solution of ascorbic acid in water for injection, for intravenous, intramuscular, or subcutaneous use. Each mL contains ascorbic acid 500 mg (2.84 mmol), edetate disodium 0.025%, and water for injection q.s. with the pH (range 5.5 to 7.0) adjusted with sodium bicarbonate, hence providing ~ 2.84 mmol sodium. The product is supplied in sterile 50 mL single use glass ampules containing 500 mg/mL of ascorbic acid USP. The stock solution contains 2.84 mmol of ascorbic acid per mL and 2.84 mmol of sodium per mL for a theoretical osmolality of 2.84 + 2.84 = 5.7 mOsm/mL.

5.2 Oxaliplatin

Chemistry:
Oxaliplatin is an antineoplastic agent with the molecular formula C8H14N2O4Pt and the chemical name of cis-[(1 R,2 R)-1,2- cyclohexanediamine-N,N'] [oxalato(2-)- O,O'] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1, 2 - diaminocyclohexane(DACH) and with an oxalate ligand as a leaving group.

Mechanism of Action:
Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter- and intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.

In vivo studies have shown antitumor activity of oxaliplatin against colon carcinoma. In combination with 5-fluorouracil, oxaliplatin exhibits in vitro and in vivo antiproliferative activity greater than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210 (leukemia)].

Pharmacokinetics:
The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases (t1/2α; 0.43 hours and t1/2β; 16.8 hours) and a long terminal elimination phase (t1/2γ; 391 hours). Pharmacokinetic parameters obtained after a single 2-hour intravenous infusion of ELOXATIN at a dose of 85 mg/m2 expressed as ultrafilterable platinum were Cmax of 0.814 mcg/mL and volume of distribution of 440 L.

Interpatient and intrapatient variability in ultrafilterable platinum exposure (AUC0–48hr) assessed over 3 cycles was moderate to low (23% and 6%, respectively). A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established.

Known Side Effects and Toxicities:
Most common adverse reactions (incidence ≥ 40%) were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. Other adverse reactions, including serious adverse reactions, have been reported.

Pharmaceutical Data:
Powder for solution for infusion: Oxaliplatin is supplied in clear, glass, single-use vials with gray elastomeric stoppers and aluminum flip-off seals containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is also present as an inactive ingredient. Store under normal lighting conditions at 25°C (77°F); excursions permitted to 15–30°C (59–86°F). Concentrate for solution for infusion: Oxaliplatin is supplied in clear, glass, single-use vials with gray elastomeric stoppers and aluminum flip-off seals containing 50 mg, 100 mg or 200 mg of oxaliplatin as a sterile, preservative-free, aqueous solution at a concentration of 5 mg/ml. Water for Injection, USP is present as an inactive ingredient. Store at 25°C (77°F); excursions permitted to 15- 30°C (59-86°F). Do not freeze and protect from light (keep in original outer carton).

Supply:
Commercially available.

5.3 Irinotecan

Chemistry:
Irinotecan hydrochloride injection is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically investigated as CPT-11. Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from

plants such as Mappia foetida and Camptotheca acuminata. The chemical name is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy- 3,14-dioxo-1H - pyrano[3',4':6,7] - indolizino[1,2 - b]quinolin - 9 - yl - [1,4'bipiperidine] - 1' - carboxylate, monohydrochloride, trihydrate.

Mechanism of Action:
Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible singlestrand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these singlestrand breaks. Current research suggests that the cytotoxicity of Irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either Irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Pharmacokinetics:
After intravenous infusion of Irinotecan in humans, Irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of Irinotecan and SN-38 are similar to those of total Irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium. Over the recommended dose range of 50 to 350 mg/m2, the AUC of Irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of Irinotecan. Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which Irinotecan and SN-38 predominantly binds is albumin.

Known Side Effects and Toxicities:
Irinotecan can induce both early and late forms of diarrhea. Both forms of diarrhea may be severe. Early diarrhea (occurring during or shortly after infusion of irinotecan) may be accompanied by cholingergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis than can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by atropine. Late diarrhea (generally occurring more than 24 hours after irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide. Severe myelosuppression may also occur with irinotecan.

Pharmaceutical Data:
Each mL of Irinotecan hydrochloride injection contains 20 mg Irinotecan (on the basis of the trihydrate salt); 45 mg sorbitol; and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). Protect from light. Do not freeze. It is recommended that the vial should remain in the

carton until the time of use.

Supply:
Commercially available.

5.5 Fluorouracil (5-FU)

Chemistry:
Fluorouracil or 5-Fluorouracil (5-FU) is a fluorinated pyrimidine differing from the normal RNA substrate, uracil, by a fluorinated number 5 carbon. The chemical has a pH of 8.1, and the commercially available solution is buffered with NaOH to obtain an alkaline solution with a pH of around 9.0. The drug is both light sensitive and will precipitate at low temperatures or, occasionally, after a prolonged period at room temperature. Melting range of the solid is 280-284°C. At 25°C the solubility is 1.2 m g/m l in chloroform. The sodium content is 8.24 mg/ml and molecular weight 130.08.

Mechanism of Action:
The metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridilic acid to thymidilic acid. In this fashion, 5-FU interferes with the synthesis of DNA. This creates a thymidine deficiency that provides unbalanced growth and cell death. Prolonged administration of 5-FU continuous infusion may favor 5-FU incorporation into RNA.

Pharmacokinetics:
5-FU is rapidly absorbed by the tissues. Studies with radioactively labeled 5-FU administered IV, have indicated passage of the drug through the blood-brain barrier. Intravenous administration gives a half-life of 5 – 7.5 minutes at a 15 mg/kg dose. Following the i.v. administration of a single 15 mg/kg dose of radioactively labeled drug, levels of 28 mcg/ml, 2-8 mcg/ml, and 0.72 mcg/ml in plasma were observed at 10 minutes, 2 hours, and 24 hours, respectively. The drug is largely catabolized in the liver and excreted in the form of nontoxic metabolites. Eighty percent of the drug is excreted as CO2 from the lungs, and approximately 15% is excreted intact in the urine in 6 hours. Of this, 90% is excreted in the first hour.

Known Side Effects and Toxicities:
Mild nausea and vomiting, stomatitis, anorexia, diarrhea, alopecia, hand/foot syndrome, myelosuppression, cerebellar ataxia, skin, and cardiac toxicity have been observed. The most common toxicities with continuous infusion 5-FU are mucositis and hand/foot syndrome.

Pharmaceutical Data:
Each 10 ml ampule contains 500 mg of the drug (50 mg/ml), adjusted to a pH of approximately 9 with sodium hydroxide. 5-FU is stored at room temperature and given over 46 hours infusion as per standard of care.

Supply:
Commercially available.

5.6 Treatment Regimen

FIRINOX REGIMEN

Given every 14 days:

- Oxaliplatin 85 mg/m2 IV over 2 hours
- Irinotecan 180 mg/m2 IV over 90 minutes
- Fluorouracil 2400 mg/m2 IV infusion over approximately 46 hours (NO BOLUS)

Based on the patient's baseline BSA, recommended 5-FU and oxaliplatin or irinotecan doses will be calculated. If the patient has a 10% or greater weight change (+/-) from baseline or from the last weight used to calculate BSA and drug doses, dose will be recalculated. Rounding the doses of 5-FU, oxaliplatin, and irinotecan is allowed as per institutional guidelines. Pre-medications and supportive medications are as per institutional practice.

Ascorbic Acid

Ascorbic acid 100 grams IV over approximately 2 hours, 2 or 3 times a week as described below. Test dose/doses of ascorbic acid will be given prior to the first cycle as per routine integrative medicine department policy once patients sign informed consent. The test dose will be ascorbic acid 50 grams IV to be given during the screening visit.

5.7 Prior and Concomitant Therapy

Prior therapy with FOLFIRINOX will exclude the patient from participation in the study.

Throughout the study, investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care.

The following therapies and treatment should not be administered while on study protocol: any investigational agent or other anti-tumor treatment (both standard and investigational) outside of protocol described therapy. Elective major surgeries during the study through 30 days after the last dose of the protocol specified treatment.

Prophylactic growth factor use is permitted as per ASCO, NCCN or institutional guidelines.

5.8 Side Effects

5.8.1 Ascorbic Acid

Possible (occurring in 10-29% of people)

- Gastrointestinal: Nausea, vomiting, abdominal cramps and diarrhea have been reported during infusion of ascorbic acid.
- Neurologic: Lightheadedness, flushing and shivering during infusion, headaches, weakness.

Rare <1%:

- Oxalate Nephropathy
- Acute Renal Failure

- Intravascular hemolysis seen in G6PD deficiency patients

5.8.2 FIRINOX:

Likely (occurring in 30% or more people):

- Anemia (low number of red blood cells)
- Bruising or bleeding
- Neutropenia
- Delayed or persistent diarrhea
- Neuropathy
- Nausea and vomiting
- Mucositis
- Cholinergic reaction (stomach cramps, diarrhea, sweats, dizziness, excess saliva, watery eyes, tiredness, and problems with vision)
- Palmar plantar erythemia
- Skin hyperpigmentation
- Increased sensitivity to sun
- Fatigue and lack of energy
- Hair thinning/loss

Possible (occurring in 10-29% of people):

- Watery eyes
- Infusion reactions
- Extravasation

Rare, but could be serious (occurring in less than 10%):

- Allergic reaction
- Chest pain or stroke

There can be treatment delays or interruptions, if needed, to make the treatment safer or more tolerable or if there are side effects as described in dose modifications.

5.9 Supportive Therapy

Antidiarrheal medications:

- Patients should be instructed to begin taking loperamide (2mg) at the earliest sign of poorly-formed or loss stools. Oral loperamide 2mg every two hours should continue until 12 hours after the last liquid stool
- Aggressive supportive care should be provided for patients with Grade 4 ANC and ≥ Grade 3 diarrhea until neutropenia and diarrhea resolve. Hospitalization for evaluation and management of complicated diarrhea, is strongly recommended.

Irinotecan-Related Cholinergic Syndrome

- Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25-1.0mg IV or SC should be used to treat these symptoms and should be used prophylactically.
- Combination anticholinergic medications containing barbiturates or other agents

(e.g. Donnatal®) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc).
- Diarrhea developing more than 24 hours after the irinotecan dose should be managed with loperamide as described above.

Antiemetic Therapy:
- Antiemetic therapy should be administered at the physician's discretion. A combination of a 5-HT# antagonist and dexamethasone is strongly recommended. Additionally, for delayed nausea, a combination of dexamethasone 4mg and ondansetron 8mg twice a day orally for three days, and prochlorperazine 10mg orally four times daily on an as needed basis for nausea are recommended.

Growth Factor Supply:
- Use of growth factor support as primary prophylaxis to prevent neutropenia is not prohibited. An ANC <1500 on day 1 of any cycle will require the use of growth factor for all remaining cycles as per NCCN/ASCO guidelines for prophylaxis of febrile neutropenia unless otherwise not indicated.
- Choice of growth factor is at the investigator's discretion
- Use of an erythropoiesis-stimulating agent is to be used at the investigator's discretion

Fever:
- Because of the risk of sepsis with FOLFIRINOX, especially in those patients who have biliary stents due to biliary obstruction, patients should call their treating physician and be evaluated as soon as possible.

Management of Laryngopharyngeal Dysesthesias:
- Oxaliplatin may cause discomfort in the larynx or pharynx associated with the sensation of dyspnea, anxiety, and swallowing difficulty.
- Exposure to cold can exacerbate these symptoms. Do not use ice chips or other forms or oral cryotherapy to decrease stomatitis in conjunction with oxaliplatin
- Anxiolytics may be used at the physician's discretion.

5.10 Preparation and Administration of Study Drug/Therapy

Ascorbic Acid Preparation:

Materials: Ascorbic acid injection (USP, 500 mg/mL) supplied by the Jefferson Pharmacy, sterile water for injection (USP, 1,000-mL IV bag), magnesium chloride injection (200 mg/mL, 20%), calcium gluconate injection (USP, 100 mg/mL, 10%), SmartSite Gravity Set®, and Microbore Extension Set (0.2µm Supor® filter), are used in the preparation of the Ascorbic Acid IV Infusion sets.

Preparation:

1. Spray the inside of the biosafety cabinet, handler's gloves and the sterile water filled 1-liter IV bag with 70% isopropyl alcohol as needed. Excess alcohol may be

pat dry with a clean paper towel.

2. Insert a sterile 16-gauge needle into the sterile water IV bag and squeeze the bag to drain 250 ml of liquid from the bag into a graduated cylinder. Remove the needle from the bag. Discard the drained liquid. This leaves 750mL of sterile water contained in the bag.
3. Attach a different sterile 16-gauge needle to another sterile 60-mL syringe
4. Draw up a 50mL injection of Ascorbic Acid (AA) into the syringe and inject into the bag.
    a. For the 75-g dosage: repeat two times, using a new sterile syringe and needle each time (150 mL AA total).
    b. For the 1 00-g dosage: repeat three times, using a new sterile syringe and needle each time (200 mL AA total).
5. Attach either a sterile 18- or 20-gauge needle to a sterile 5-mL syringe.
6. Draw up 5 mL of Magnesium Chloride (MgCl) into the syringe and inject into the bag (5mL total for both concentrations)
7. Attach a separate sterile 18- or 20-gauge needle to a sterile 1 0-mL syringe.
    a. For the75-g dosage: stop here (10 mL CaGluc total)
    b. For the 100-g dosage: repeat one more time, using a new sterile syringe (20 mL CaGluc total)
8. Mix the solution well by inversion.
9. Place the bag in a hanging position. Aseptically connect the sterile IV tubing and .2µm filter to the bag and allow to drip/infuse into the patients line.

Total volume:

75g Bag	**100g Bag**
750mL water	750mL water
150mL AA	200mL AA
5mL MgCL	5mL MgCl
10mL CaGluc	20 mL CaGluc
915mL total volume	975mL total volume

5.11 Receiving, Storage, Dispensing and Return

Receipt of Drug Supplies:
Ascorbic Acid Injection USP is ordered though the Thomas Jefferson University Pharmacy.

Storage:
The product is stored in a carton protected from light between 2-8°C. It must not be frozen. It must be infused within 4 hours of preparing diluted solutions for injection.

Dispensing of Study Drug:
Regular study drug reconciliation will be performed to document drugs were given as per protocol. Since all the drugs involved are intravenous, there will not be a drug log for patients to fill out.

Return or Destruction of Study Drug:
Drug will not be returned or destroyed.

6.0 STUDY PROCEDURES

6.1 Study Visit Schedule

See Appendix A.

Screening visit (-28 to day 0):
Patient will meet with one of the investigators and coordinator to review informed consent. Once patient signs consent form, coordinator will review the eligibility criteria, review medical history, document concomitant medications and ECOG PS. Physical exam including vital signs (height, temperature, pulse, heart rate, and blood pressure) and weight will be recorded. Baseline labs, pregnancy test (urine or blood), G6PD level, EKG, urinalysis and imaging scans will be performed. Scans should be done within 28 days of study entry.

Test dose/doses of ascorbic acid (50 grams IV) will be given prior as per routine integrative medicine department policy once patients sign informed consent but before the first cycle of FIRINOX. Please see table 1 for ascorbic acid infusions.

Baseline:
Patient will fill out EORTC QLQ C30, CIPN 20, oxaliplatin neuropathy scale, FACIT fatigue scale and SGA. These forms can be filled out during the test dose/doses of ascorbic acid infusion prior to cycle 1

Study visits:
Review medications, AE assessment, symptom directed exam, vital signs, ECOG PS, chemistry, hematology, EORTC QLQ-C 30

End of Treatment Study Procedures:
Review medications, AE assessment, complete physical, exam, vital signs, ECOG PS, chemistry, hematology, EORTC QLQ-C 30, EORTC CIPN 20, oxaliplatin neuropathy scale, FACIT fatigue scale, SGA.

Post-Treatment/Follow-up:
Patients will be followed once every 14-28 days after last treatment for a post treatment/follow up assessment.

Review medications, AE assessment, complete physical, exam, vital signs, ECOG PS, chemistry, hematology, EORTC QLQ-C 30, EORTC CIPN 20, oxaliplatin neuropathy scale, FACIT fatigue scale, SGA. If patient is not able to come for an office appointment, a telephone follow up will be attempted. If patient refuses to follow up or is lost to follow up or dies within 30 days, it will be documented in the chart.

6.2 Subject Compliance Monitoring

Since all treatment is intravenous, subjects will be closely monitored at the time of their visits. Patients will be evaluated by the treating oncologist at each chemotherapy visit to

evaluate for adverse events and compliance to the protocol will be assessed regularly by the PI. The investigator at Integrative Medicine will be responsible for monitoring infusion of ascorbic acid in the Myrna Brind Center at Thomas Jefferson University. A chart will be maintained at the center to record the time, dose and unexpected side effects which will be reviewed every 3 months by the PI.

6.3 Definition of Dose-Limiting Toxicities

- Any Grade 5 event attributable to the regimen
- Any Grade 4 non-hematological toxicity that is attributable to regimen with the exception of alopecia, diarrhea, nausea and vomiting
- Nausea, vomiting or diarrhea ≥Grade 3 that persists for greater than 72 hours despite optimal antiemetic and anti-diarrheal therapy and IV hydration
- Any Grade 3 non-hematological toxicity that is study drug related that results in delay of chemotherapy by greater than 2 weeks

Dose De-escalation Schedule	
Dose Level	**Dose of Intravenous ascorbic acid**
Level 1	100 grams
Level -1	75 grams
Level -2	50 grams

6.4 Dose Delays and Dose Modifications

If a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level. If chemotherapy is on hold due to side effects clearly attributable to it, ascorbic acid can continue on schedule without any dose modifications.

Dose modifications for FIRINOX:

Neutrophil number	**5FU**	**Irinotecan**	**Oxaliplatin**
>/= 1500	2400 mg/m^2	180 mg/m^2	85 mg/m^2
1000-1500 or if patient had • Febrile neutropenia • Grade 3 /4 infection • Grade 4 neutropenia >7 days	2400 mg/m^2	150 mg/m^2	85 mg/m^2
Less than 1000 on day of treatment	Hold	Hold	Hold

Primary prophylactic GCSF strongly recommended as per NCCN/ASCO/institutional guidelines. Reevaluate weekly if treatment is held.

Platelets	5FU	Irinotecan	Oxaliplatin
>/= 100,000	2400mg/m^2	180 mg/m2	85 mg/m^2
75,000 to 100,000	1800mg/m^2	150 mg/m^2	60 mg/m^2
Less than 75,000	Hold	Hold	Hold

Reevaluate weekly. If counts have not recovered after a delay of two weeks, despite appropriate supportive measures, it is recommended that treatment be stopped.

Renal Impairment CrCL Dose (% of original):

Renal Impairment	CrCL	Dose
5FU	No change	No change
Irinotecan	No change	No change
Oxaliplatin	<20	Contraindicated

Hepatic Impairment

Drug	Bilirubin	Dose
5FU	</=3	No change
	>3	Avoid
Irinotecan	1- 1.5	135mg/m2
	1.5 to 3	90mg/m2
	>/=3	Avoid
Oxaliplatin	</=3	No change
	>3	Avoid

Diarrhea

CTCAE 4.03 grade 1 or 2 diarrhea occurring between cycles does not necessitate dose modification, unless accompanied by fever or neutropenia. If the diarrhea is more than grade 2 on day of treatment, delay treatment by 7 days and reassess. Dose adjust 5FU and irinotecan as below

Diarrhea	5FU	Irinotecan	Oxaliplatin
Grade 1	2400mg/m^2	150mg/m^2	85mg/m^2
Grade 2	1800mg/m^2	135mg/m^2	85mg/m^2
Grade 3 or higher	Hold	Hold	Hold

Fluorouracil-Specific Dose Modifications:

If a Grade 3 or 4stomatitis occurs, reduce the fluorouracil infusion doses to 75% of the original dose. For a Grade 3 or 4 Palmer-Plantar Erythrodysesthesia, reduce the fluorouracil infusion doses to 75% of the original dose.

Oxaliplatin-Specific Dose Modifications:
If the neurosensory toxicity is CTCAE Grade 1 or 2 and last < 7 days, administer the full dose of oxaliplatin. If the toxicity is CTCAE Grade 2 and persists 7 or more days, reduce the oxaliplatin dose to 60mg/m^2. Oxaliplatin should be discontinued for neurosensory toxicities CTCAE Grade 3 or above and 5FU and Irinotecan can continue to be given.

Peripheral Neuropathy	**5FU**	**Irinotecan**	**Oxaliplatin**
Grade 1	2400mg/m^2	180mg/m^2	85mg/m^2
Grade 2	2400mg/ m^2	180mg/m^2	60mg/m^2
Grade 3 or higher	2400mg/m^2	180mg/m^2	Hold

For transient cold-related dysesthesia or paresthesia without pain, there is no need to delay or reduce oxaliplatin. For acute laryngopharygeal dysesthesia, increase the infusion time to 4 hours.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

8 patients as described below.

7.2 Statistical Methods

The study will follow a Phase I design for toxicities called the time-to-event continual reassessment method (TITE-CRM). (Cheung & Chappell, 2000; Normolle & Lawrence, 2006) We will enroll 8 patients with toxicities monitored for 28 days. We expect to enroll one patient a month on average. The first patient will be started at the highest dose. Previous studies suggest that the probability of toxicity at the highest dose is less than 10% and so we assume prior probabilities of toxicity 0.02, 0.04, and 0.08 for the three dose levels of 50grams, 75grams, and 100grams, respectively. Assigned dose will be administered three times per week of treatment with the target probability of toxicity for the optimal dose is 0.10. Results from 1000 simulated data sets when the true toxicities match our assumptions indicate selection of the highest dose 93.2% of the time with an expected sample sizes of 0.60, 1.08, and 6.24 for the three doses and 0.50 toxicities expected at the highest dose.

Change in quality of life over the six measurement times will be modeled using mixed effects linear regression to account for correlation among repeated measurements from the same subjects. Average change in QoL from baseline to follow-up will be computed. Assuming at least 6 patients receive the highest dose, we expect 80% power to detect an effect size of 3.19 (average change in global QoL score of 1.44 standard deviations) using a two-sided paired t-test with alpha=0.05.

7.3 Subject Population(s) for Analysis

Patients who received at least 2 cycles of FIRINOX will be included in the final

analysis. If a patient comes off study earlier than 2 cycles of FIRINOX for any reason other than DLT, those patients will be replaced so that adequate number of QOL questionnaires can be collected. All patients who receive at least one dose of intravenous ascorbic acid will be followed for safety but will not be included for analysis of TITE-CRM if they received less than 2 cycles.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event:

Adverse events are classified as serious or non-serious.

A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.2 Adverse Event Reporting

Adverse Event Reporting Period:

The study period which adverse events must be reported is normally defined as the period from the initiation for any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following

the last administration of study treatment.

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

General Physical Examination Findings:
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-Study Adverse Event:
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values:
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery:
Any adverse event that results in hospitalization or prolonged hospitalization should be documents and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or

diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.3 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded in the CRF

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.4 Stopping Rules

We will review data after 4 patients are enrolled on the study and receive at least one dose of intravenous ascorbic acid. If 2 out of the 4 cannot complete 2 cycles of FIRINOX then we will halt the study and discuss a corrective plan in the GI MDG. The SKCC DSMB will follow all patients and monitor all AEs as per institutional guidelines.

8.5 Data and Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will included careful assessment and appropriate reporting of adverse events as noted above, as well as the compliance and implementation of the SKCC data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events by both the assigned Medical Monitor and the SKCC DSMC.

8.5.1 Medical Monitoring and AE/SAE Reporting

A Medical Monitor is assigned to this study at the Thomas Jefferson University. This is a physician/pharmacist who is not directly involved in the trial, and is not currently collaborating with the sponsor/investigator on any other trial. The role of the Medical Monitor is to review all reportable AEs/SAEs (in real-time) including grading, toxicity assignments, non-reportable AEs (quarterly), protocol violations/deviations, as well as all other safety data and activity data observed in the ongoing clinical trial occurring at Thomas Jefferson University. The Medical Monitor may recommend reporting of adverse events and relevant safety data, and may also recommend suspension or

termination of the study to the DSMC and TJU IRB.

Every SKCC investigator initiated protocol includes requirements for reporting of adverse events based on CTC 4.0. All events are reported to the IRB and Medical Monitor using a password protected web-site. In addition all unexpected and serious adverse events (SAEs) are reported to the TJU IRB and to the Food and Drug Administration (FDA) if applicable. The investigator is required to submit all unexpected and serious adverse events to the TJU IRB and the Medical Monitor within the timeframes outlined in the below table. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, if the Medical Monitor determines corrective action is necessary, an "ad hoc" DSMC meeting will be called. Fatal adverse events related to treatment which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days. A summary of the reporting requirements for SKCC investigator initiated Phase I and Phase II studies are presented below.

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 and 5
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 - 48 Hours (Death: 24 Hour Phase 2 - 5 Working Days
Possible Probable Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 working days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase 1 - 48 Hours Phase 2 - 5 Working Days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 and Phase 2 - 48 Hours (Death: 24 Hours)

** NOTE: This table is based on the NCI AE/SAE reporting Guidelines and the TJU IRB Policy and Procedures. Please follow the individual protocol AE/SAE reporting guidelines if more stringent reporting procedures are specified.

If an IND study, the participating site will also be responsible for completing FDA MedWatch 3500A Form and send to TJU Study Coordinator and IND holder/designated personnel for submission to the FDA.

<u>Safety Reporting Requirements for IND Holders:</u>
In accordance with 21 CFR 212.32, sponsor-investigator of studies conducted under an IND must comply with following safety reporting requirements:

Expedited IND Safety Reports:
7 Calendar-Day Telephone or Fax Report:
The Sponsor-Investigator is required to notify the FDA of any fatal or life- threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of intravenous ascorbic acid. An unexpected adverse event is one that is not already described.

Such reports are to be telephoned or faxed to the FDA within 7 calendar days and to the IRB within 24 hours of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:
The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of ascorbic acid. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

FDA fax number for IND Safety Reports:1 (800) FDA – 0178

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to:

Thomas Jefferson University IRB

IND Annual Reports:
In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to TJU IRB. Copies of such reports should be mailed to:

8.5.2 Data and Safety Monitoring Committee

Data and Safety Monitoring Committee (DSMC) is the Data and Safety Monitoring Board (DSMB) for the SKCC. The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct,

progress, validity, and integrity of the data for all clinical trials at the Thomas Jefferson University SKCC. The committee meets quarterly to review the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

- The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call) within 24 hours following the notification of an unexpected adverse event felt to be related to the study drug.
- Prior to each DSMC meeting, each board member, is provided a printout of all reported AEs and SAEs occurring during the reporting period for this clinical trial. The principal investigator provides a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment, a written report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol, as well as recommendations from the Medical Monitor. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.
- A summary of the board's action is sent to each investigator, the CCRRC and TJU IRBs. The DSMC actions may include recommendations/requirements that will lead to improved patient safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC may also take note of slow accrual or lack of scientific progress, and refer such issues to the Protocol Review Committee (PRC). The DSMC provides the investigator with the rationale for any decision made.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the formal discontinuation of clinical trial. These documents should be retained for a longer period if required.

10.0 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

<u>SKCC Investigator Initiated Phase I Studies</u>

Phase I studies require continuous monitoring by the PI of the study with quarterly safety and monitoring reports submitted to the CTO and the DSMC. Each protocol is assigned to a medical monitor (a physician or other member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial). The medical monitor reviews all adverse events (in addition to unexpected adverse events), safety data and activity data observed in the ongoing clinical trial at each new dose level, prior to dose escalation.

The PI provides a report to the DSMC of all AE/SAEs, safety and toxicity data, and any

corrective action that occurred on a quarterly basis. The medical monitor also provides a summary of their review. The summary of all discussions of adverse events are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place quarterly. Patients are only identified by initials, and no other personal health information (PHI) is included in the reports.

The medical monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data observed throughout the life of a clinical trial. In such circumstances, and "ad hoc" DSMC meeting will be called to discuss corrective action with the PI. If for any reason the PI of the trial disagrees with the conclusions of the Medical Monitor or DSMC, the issue will be referred to the Associate Director of Clinical Investigations, who will be responsible for dispute resolution.

The summary of all discussions of adverse events are included in the SKCC investigator's reports to the TJU IRBs as part of its annual progress report. The DSMC and the TJU IRBs may, based on the monitor's recommendation suspend or terminate the trial. The quarterly safety and monitoring reports include a statement as to whether this data has invoked any stopping criteria in the clinical protocol.

The investigator is required to submit all unexpected on-site adverse events and serious adverse events (SAEs) to the TJU IRB and the DSMB within 48 hours. Fatal adverse events which are unexpected must be reported within 24 hours to the TJU IRB and the DSMB. Fatalities not related to the study drug/device must be reported within 5 days.

Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.1.1 Independent External and Internal Audits

All studies initiated by SKCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, PRC and/or the Director of Clinical Investigations, SKCC. Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or PRC based on prior findings, allegations of scientific misconduct and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CTO randomly audits at least 10 percent of all patients entered into therapeutic SKCC trials and other trials as necessary, on at least a bi-annual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the PRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.0 STUDY FINANCES

12.1 Funding Source

Financing of this study will be via the Myrna Brind Foundation Special Purpose Fund and the Department of Medical Oncology.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by the institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and

approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

12.3 Subject Stipends or Payments

Patients will not be paid any stipends to participate in this clinical trial.

13.0 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the principal investigator and the University. Every effort will be made to publish the results of this clinical trial in peer reviewed scientific journals by the principal investigators or co-investigators.

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15.0 APPENDICES

Appendix 1: Study Procedures/Study Visit Schedule

Procedures		**Screening (Day –28o 0)**	**Baseline (Day -28 to 0)**	**Study Visit 1* (Day 0 ±3) CYCLE 1**	**Study Visit 2* (Day 15 ± 3) CYCLE 2**	**Study Visit 3*(Day 29± 3) CYCLE 3**	**Study Visit 4* (Day 43± 3) CYCLE 4**	**Study Completion/EOT**	**Follow up/ Post treatment**
Signed Consent Form		X							
Assessment of Eligibility Criteria		X							
Review of Medical History, demographics		X							
Review of Concomitant Medications		X		X	X	X	X	X	X
Study Intervention				X	X	X	X		
Physical Examination	*Complete*	X						X	X
	Symptom-Directed			X	X	X	X		
	Vital Signs (Temperature, Pulse, HR, BP and weight)	X[e]		X	X	X	X		
ECOG PS		X		X	X	X	X	X	X
Assessment of Adverse Events				X	X	X	X	X	X

Procedures		Screening (Day –28 to 0)	Baseline (Day -28 to 0)	Study Visit 1* (Day 0 ±3) Cycle 1	Study Visit 2* (Day14 ± 3) Cycle 2	Study Visit 3*(Day 28 ± 3) Cycle 3	Study Visit 4* (Day 4 ± 3) Cycle 4	Study Completion/EOT	Follow up post treatment
Clinical Laboratory	*Pregnancy test^, PT, PTT*	X							
	Chemistry[a]	X		X	X	X	X	X	X
	Hematology[b]	X		X	X	X	X	X	X
	Urinalysis, G6PD level, EKG	X							
	GI tumor marker	X			X		X		
	Imaging [C]	X[#]					X		
Other Procedures [d]	*EORTC QLQC 30*		X	X	X	X	X	X	X
	EORTC CIPN 20		X		X		X	X	X
	Oxaliplatin neuropathy scale		X		X		X	X	X
	FACIT fatigue scale		X				X	X	X
	SGA		X				X	X	X
Treatment	*FIRINOX*			X	X	X	X		
	Ascorbic Acid Test Dose[f]	X							

Ascorbic acid will be given as per the table below. No other study related procedures will be performed on the day of ascorbic acid infusion

Example schema:

Monday	D1 - FIRINOX	D8 - Ascorbic acid
Tuesday	D2 - 5FU	D9
Wednesday	D3 - 5FU disconnect + Ascorbic acid	D10 - Ascorbic acid
Thursday	D4	D11
Friday	D5 Ascorbic acid	D12 - Ascorbic acid
Saturday	D6	D13

Sunday	D7	D14

Abbreviations: HR=Heart rate, BP=Blood Pressure, ECOG=Eastern Cooperative Oncology Group, PT=Prothrombin Time, PTT=Partial thromboplatin time, G6PD=Glucose 6 Phosphatase deficiency, EKG= Electrocardiogram, GI= Gastrointestinal, EORTC= European Organization for Research and Treatment of Cancer, QLQ= Quality of Life Questionnaire, CIPN= Chemotherapy Induced Peripheral Neuropathy, FACIT= Functional Assessment of Chronic Illness Therapy), SGA= Subjective Global Assessment, FIRINOX = 5FU+IRInotecan+Oxaliplatin

$ Any evaluation can be omitted if done within 72 hours

* Study visit 1-4 repeated every 4 cycles

** Not mandatory

Baseline scans within 28 days of screening.

^ Only for premenopausal females. Serum or urine is acceptable

a CMP, LDH

b CBC with differential

c CT of chest, abdomen and pelvis recommended every 8 weeks (± 1 week). MRI of abdomen can be performed if clinically appropriate instead of CT scan

d QOL questionnaires can be performed during ascorbic acid infusions.

e Height will be calculated at baseline for BSA measurement.

f. test dose of ascorbic acid is 50 grams IV

Appendix 2: ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 3 EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4: EORTC CIPN 20

1. Did you have tingling fingers or hands?[a]
2. Did you have tingling toes or feet?[a]
3. Did you have numbness in your fingers or hands?[a]
4. Did you have numbness in your toes or feet?[a]
5. Did you have shooting or burning pain in your fingers or hands?[a]
6. Did you have shooting or burning pain in your toes or feet?[a]
7. Did you have cramps in your hands?[b]
8. Did you have cramps in your feet?[b]
9. Did you have problems standing or walking because of difficulty feeling the ground under your feet?[a]
10. Did you have difficulty distinguishing between hot and cold water?[a]
11. Did you have a problem holding a pen, which made writing difficult?[b]
12. Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?[b]
13. Did you have difficulty opening a jar or bottle because of weakness in your hands?[b]
14. Did you have difficulty walking because your feet dropped downwards?[b]
15. Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?[b]
16. Were you dizzy when standing up from a sitting or lying position?[c]
17. Did you have blurred vision?[c]
18. Did you have difficulty hearing?[a]

Please answer the following question only if you drive a car

19. Did you have difficulty using the pedals?[b]

Please answer the following question only if you are a man

20. Did you have difficulty getting or maintaining an erection?[c]

Appendix 5: Oxaliplatin associated neuropathy questionnaire

Table 4 – Oxaliplatin-associated Neuropathy Questionnaire (2005).

– Do you have...			If you had symptoms during last cycle...									
			... how much of the symptoms did you have?[a]					... did the symptoms affect your daily activities?[b]				
1. UPPER EXTREMITY SYMPTOMS												
...tingling (pin and needles)?	No	Yes	1	2	3	4	5	1	2	3	4	5
... numbness?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in telling the difference between rough and smooth surfaces?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in feeling hot things?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in feeling cold things?	No	Yes	1	2	3	4	5	1	2	3	4	5
... a greater than normal sense of touch (i.e. putting on gloves)?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning pain or discomfort without cold?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning pain or discomfort with cold?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in identifying objects in your hand (i.e. coins)	No	Yes	1	2	3	4	5	1	2	3	4	5
... involuntary hand movements?	No	Yes	1	2	3	4	5	1	2	3	4	5
2. LOWER EXTREMITY SYMPTOMS												
...tingling (pin and needles)?	No	Yes	1	2	3	4	5	1	2	3	4	5
... numbness?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in telling the difference between rough and smooth surfaces?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in feeling hot things?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in feeling cold things?	No	Yes	1	2	3	4	5	1	2	3	4	5
... a greater than normal sense of touch (i.e. discomfort with socks)?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning pain or discomfort without cold?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning pain or discomfort with cold?	No	Yes	1	2	3	4	5	1	2	3	4	5
... a feeling of heaviness in your legs?	No	Yes	1	2	3	4	5	1	2	3	4	5
3. ORAL/FACIAL SYMPTOMS												
... jaw pain?	No	Yes	1	2	3	4	5	1	2	3	4	5
... eyelids dropping?	No	Yes	1	2	3	4	5	1	2	3	4	5
... throat discomfort?	No	Yes	1	2	3	4	5	1	2	3	4	5
... ear pain?	No	Yes	1	2	3	4	5	1	2	3	4	5
... tingling in mouth?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty with speech?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning or discomfort in your eyes?	No	Yes	1	2	3	4	5	1	2	3	4	5
... loss of any vision?	No	Yes	1	2	3	4	5	1	2	3	4	5
... feeling shock/pain down back?	No	Yes	1	2	3	4	5	1	2	3	4	5
... problems with breathing?	No	Yes	1	2	3	4	5	1	2	3	4	5

Adapted from the original version. See Leonard et al.[12]

a In order to rate this item, a progressive scale is provided, in which: **1 stands for 'Hardly any', 5 stands for ' Very much'.**

b In order to rate this item, a progressive scale is provided, in which: **1 stands for 'Hardly at all bothered', 5 stands for 'Extremely bothered'.**

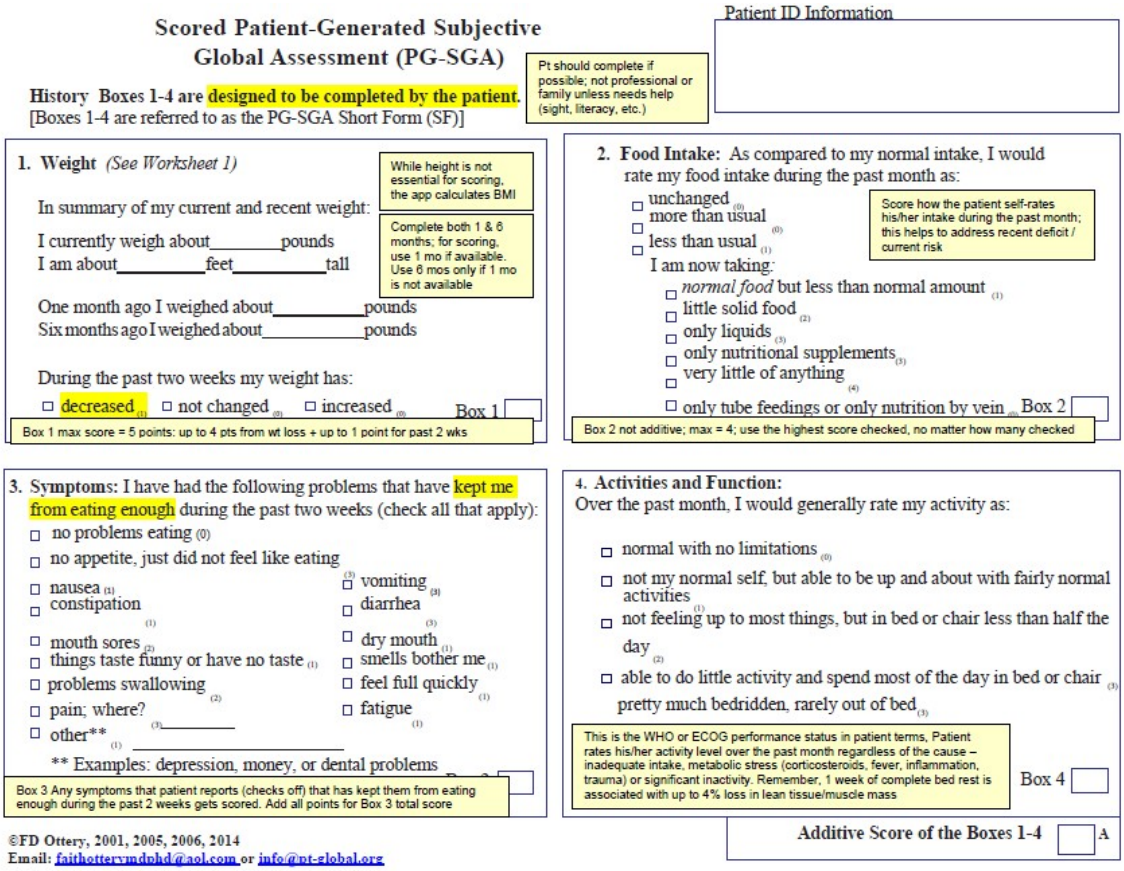
Appendix 6: FACIT fatigue scale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 7: PG-SGA questionnaire



Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

Pt should complete if possible; not professional or family unless needs help (sight, literacy, etc.)

History Boxes 1-4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

1. Weight *(See Worksheet 1)*

While height is not essential for scoring, the app calculates BMI

In summary of my current and recent weight:

Complete both 1 & 6 months; for scoring, use 1 mo if available. Use 6 mos only if 1 mo is not available

I currently weigh about_____pounds
I am about_____feet_____tall

One month ago I weighed about_____pounds
Six months ago I weighed about_____pounds

During the past two weeks my weight has:
□ decreased (1) □ not changed (0) □ increased (0) Box 1

Box 1 max score = 5 points: up to 4 pts from wt loss + up to 1 point for past 2 wks

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:

Score how the patient self-rates his/her intake during the past month; this helps to address recent deficit / current risk

□ unchanged (0)
□ more than usual (0)
□ less than usual (1)

I am now taking:
□ *normal food* but less than normal amount (1)
□ little solid food (2)
□ only liquids (3)
□ only nutritional supplements (3)
□ very little of anything (4)
□ only tube feedings or only nutrition by vein (0) Box 2

Box 2 not additive; max = 4; use the highest score checked, no matter how many checked

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):

□ no problems eating (0)
□ no appetite, just did not feel like eating (3)
□ nausea (1)
□ constipation (1)
□ mouth sores (2)
□ things taste funny or have no taste (1)
□ problems swallowing (2)
□ pain; where? (3)_____
□ other** (1)_____
□ vomiting (3)
□ diarrhea (3)
□ dry mouth (1)
□ smells bother me (1)
□ feel full quickly (1)
□ fatigue (1)

** Examples: depression, money, or dental problems

Box 3 Any symptoms that patient reports (checks off) that has kept them from eating enough during the past 2 weeks gets scored. Add all points for Box 3 total score

4. Activities and Function:
Over the past month, I would generally rate my activity as:

□ normal with no limitations (0)
□ not my normal self, but able to be up and about with fairly normal activities (1)
□ not feeling up to most things, but in bed or chair less than half the day (2)
□ able to do little activity and spend most of the day in bed or chair (3)
pretty much bedridden, rarely out of bed (3)

This is the WHO or ECOG performance status in patient terms, Patient rates his/her activity level over the past month regardless of the cause – inadequate intake, metabolic stress (corticosteroids, fever, inflammation, trauma) or significant inactivity. Remember, 1 week of complete bed rest is associated with up to 4% loss in lean tissue/muscle mass

Box 4

Additive Score of the Boxes 1-4 A

Email: faithotterymdphd@aol.com or info@pt-global.org

The remainder of this form is to be completed by your doctor, nurse, dietitian, or therapist. Thank you.

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Worksheet 1 - Scoring Weight (Wt) Loss

To determine score, use 1 month weight data if available. Use 6 month data only if there is no 1 month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point

Wt loss in 1 month	Points	Wt loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10 -19.9%
3-4.9%	2	6 - 9.9%
2-2.9%	1	2 - 5.9%
0-1.9%	0	0 - 1.9%

Numerical score from Worksheet 1 ☐

Additive Score of the Boxes 1-4 (See Side 1) ☐ A

5. Worksheet 2 - Disease and its relation to nutritional requirements

All relevant diagnoses (specify) _____

Primary disease stage (circle if known or appropriate) I II III IV Other _____

One point each:

☐Cancer ☐AIDS ☐Pulmonary or cardiac cachexia ☐Presence of decubitus, open wound, or fistula
☐Presence of trauma ☐Age greater than 65 years ☐Chronic renal insufficiency

Numerical score from Worksheet 2 ☐ B

6. Work Sheet 3 - Metabolic Demand

Score for metabolic stress is determined by a number of variables known to increase protein & calorie needs. The score is additive so that a patient who has a fever of > 102 degrees (3 points) and is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points

Fever: Score fever intensity or duration, whichever is greater. (99°F= 37.2°C 101°=38.3° and 102° = 38.9°)

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	>99 and <101	≥101 and <102	≥102
Fever duration	no fever	<72 hrs	72 hrs	> 72 hrs
Corticosteroids	no corticosteroids	low dose (<10mg prednisone equivalents/day)	moderate dose (≥10 and <30mg prednisone equivalents/day)	high dose steroid (≥30mg prednisone equivalents/day)

Numerical score from Worksheet 3 ☐ C

Even short term use of corticosteroids can adversely impact protein status and muscle mass

See www.pt-global.org for prednisone equivalents chart and metric and additional language version (as available)

7. Worksheet 4 - Physical Exam

Physical exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid status. Since this is subjective, each aspect of the exam is rated for degree of deficit. Muscle deficit impacts point score more than fat deficit. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate 3+ = severe

Muscle Status:					Fluid Status:				
clavicles (pectoralis & deltoids)	0	1+	2+	3+		0	1+	2+	3+
interosseous muscles	0	1+	2+	3+		0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+					
Global muscle status rating	**0**	**1+**	**2+**	**3+**					
orbital fat pads	0	1+	2+	3+					
triceps skin fold	0	1+	2+	3+					
Global fat deficit rating	**0**	**1+**	**2**	**3+**					

These are examples of areas that can/should be considered in determining loss/deficit (or excess fluid). RELAX... One does NOT have to assess all of these to have a global sense for loss or deficit of muscle or fat. Remember the maximum point score for physical exam is only 3 points and you are not likely to be off by more than 1 point...

Numerical score from Worksheet 4 ☐ D

Total PG-SGA score ☐
(Total numerical score of A+B+C+D above)
(See triage recommendations below)

Global PG-SGA rating (A, B, or C) = ☐

Clinician Signature _____ RD RN PA MD DO Other____ Date _____

Worksheet 5 - PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	Well nourished	Moderately malnourished	Severely malnourished
Weight	No wt loss OR Recent wt gain	<5% wt loss in 1 month (or 10% in 6 mos) OR Progressive wt loss	> 5% wt loss in 1 month (or >10% in 6 mos) OR Progressive wt loss
Nutrient intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None OR Significant recent improvement allowing adequate intake	Present of nutrition impact symptoms (PG-SGA Box 3)	Present of nutrition impact symptoms (PG-SGA Box 3)
Functioning	No deficit OR Recent improvement	Moderate functional deficit OR Recent deterioration	Severe functional deficit OR recent significant deterioration
Physical Exam	No deficit OR Chronic deficient but tissue, recent improvement	Evidence of mild to moderate loss of muscle mass / SQ fat / muscle lost on palpation	Obvious signs of malnutrition (e.g., severe loss muscle, SQ possible edema)

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage).
First line nutrition intervention includes optimal symptom management.

Triage based on PG-SGA point score

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).
≥9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

Worksheet 5 May be helpful to circle relevant statement for each

Appendix 8: AE log

Clinical Research Management Office
Adverse Event Tracking Log

Patient Name: Study Agents: ____ascorbic acid, FOLFIRINOX

Protocol: _____ Cycle/ Week #:_____

Adverse Event	Grade	☒ If started prior to tx initiation	Start Date	End Date	Continuing ?	Relationship to Treatment	Relationship to Study Drug	SAE?	Action(s) Taken	Comments

Grade: Use CTCAE Version 4

Relationship: Definite, Probable, Possible, Unlikely, Unrelated

Reviewed and Approved

PI Signature: _____

Date: _____