LUN 229
Double-Blind Randomized Phase II Trial of Carboplatin and Pemetrexed with or without OGX-427 in Patients with Previously Untreated Stage IV Non-Squamous-Non-Small-Cell Lung Cancer (The Spruce Clinical Trial)

SARAH CANNON RESEARCH INSTITUTE DEVELOPMENT INNOVATIONS PROTOCOL NUMBER:	LUN 229
STUDY DRUG:	OGX-427
SPONSOR:	Sarah Cannon Research Institute (SCRI) Development Innovations (SCRI Innovations) 3322 West End Avenue , Suite 900 Nashville, TN 37203 877-MY-1-SCRI
STUDY CHAIR:	David R. Spigel, M.D. Sarah Cannon Research Institute 3322 West End Avenue, Suite 900 Nashville, TN 37203 877-MY-1-SCRI asksarah@scresearch.net
MEDICAL MONITOR:	John D. Hainsworth, M.D. Sarah Cannon Research Institute 3322 West End Avenue , Suite 900 Nashville, TN 37203 877-MY-1-SCRI
DATE FINAL:	14 February 2013 (Version 1.0)
AMENDMENT 1 DATE:	21 March 2013 (Version 2.0)
AMENDMENT 2 DATE:	9 July 2013 (Version 3.0)
AMENDMENT 3 DATE:	05 November 2014 (Version 4.0)

Clinical Trial Statement of Compliance

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
- **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Principal Investigator (PI), I am in agreement and understand my responsibilities as a PI to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, I understand and agree that any changes I initiate without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

Clinical Trial History of Amendments

Double-Blind Randomized Phase II Trial of Carboplatin and Pemetrexed with or without OGX-427 in Patients with Previously Untreated Stage IV Non-Squamous-Non-Small-Cell Lung Cancer
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Amd #/ Amd Date	Refer to this Section	Summary
3 – 05 Nov 2014	**Synopsis Inclusion and 3.1 Inclusion Criteria**	2. ~~Recurrent Stage IV~~ **Metastatic** disease **at the time of study entry** (according to American Joint Committee on Cancer (AJCC) staging system, v7.0). 3. No prior systemic chemotherapy, immunotherapy, targeted therapy, or biological therapy **for metastatic disease**. Previous adjuvant **or neoadjuvant** therapy **for Stage I, II, or III disease** is allowed as long as the interval from **the end of treatment** ~~adjuvant therapy~~ until disease progression was >12 months. 4. No prior radiation therapy to the whole pelvis or to ≥25% of the total bone marrow area. **Other r**adiation therapy must be completed at least 2 weeks prior to **study entry** ~~randomization~~. Must have recovered from acute adverse effects prior to **study entry** ~~randomization~~.
	Section 3.2 Exclusion Criteria	8. Active second malignancy (except non-melanomatous skin or superficial bladder cancer) defined as requiring current need for cancer therapy or at high risk of recurrence **(>3~~5~~0%)** during the study.
	Section 5.1 Treatment Plan	• a corticosteroid (dexamethasone 8-**12** mg or corticosteroid equivalent) Carboplatin, at a dose calculated to produce an AUC of 6 will be administered by intravenous infusion according to institutional standards beginning ~~approximately 30 minutes~~ after the end of the pemetrexed infusion.
	Section 6.1 Hematologic Toxicity	Blood counts will be obtained at the beginning of each cycle. To start a new treatment cycle, the patient must have the following blood counts: ANC ≥1500/μL and platelet count ≥100,000/μL. **Hematologic dose modifications apply only to Day 1 values of each cycle. Dose reductions are not based on nadirs occurring during the previous treatment cycle.** Table 5 Title change: **Day 1** Hematologic Dose Modifications

Amd #/ Amd Date	Refer to this Section	Summary
	Section 6.2 Table 6 Non-Hematologic Toxicity Dose Modifications	Creatinine Clearance as calculated by Cockcroft-Gault method for Grades 2-4 toxicity criteria inserted.
	Section 8.1.3 Precautions and Risks Associated with OGX-427	Very likely: • **On rare occasions, infusion reactions can be life-threatening.** Rare: • **Anaphylaxis or severe infusion reaction**
	Section 10.2.2 Stratification Factors	Smoking Status: Patients will be stratified as smokers or non-smokers. Patients with a lifetime history of <100 cigarettes are stratified as non-smokers. Patients with ~~>10 pack/year~~ history of smoking ~~who~~ but have not smoked for >15 years are also considered non-smokers**. All others will be classified as smokers.**
	Minor edits	A 7 day window has been added to restaging after every 2 treatment cycles during initial treatment and maintenance. Innovation has been corrected to Innovations throughout. Previous protocols mentioned in the document have been labeled with their version numbers.

SCRI DEVELOPMENT INNOVATIONS

Clinical Trial Principal Investigator Signature Form

Double-Blind Randomized Phase II Trial of Carboplatin and Pemetrexed with or without OGX-427 in Patients with Previously Untreated Stage IV Non-Squamous-Non-Small-Cell Lung Cancer
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SCRI INNOVATIONS PROTOCOL NUMBER:	LUN 229
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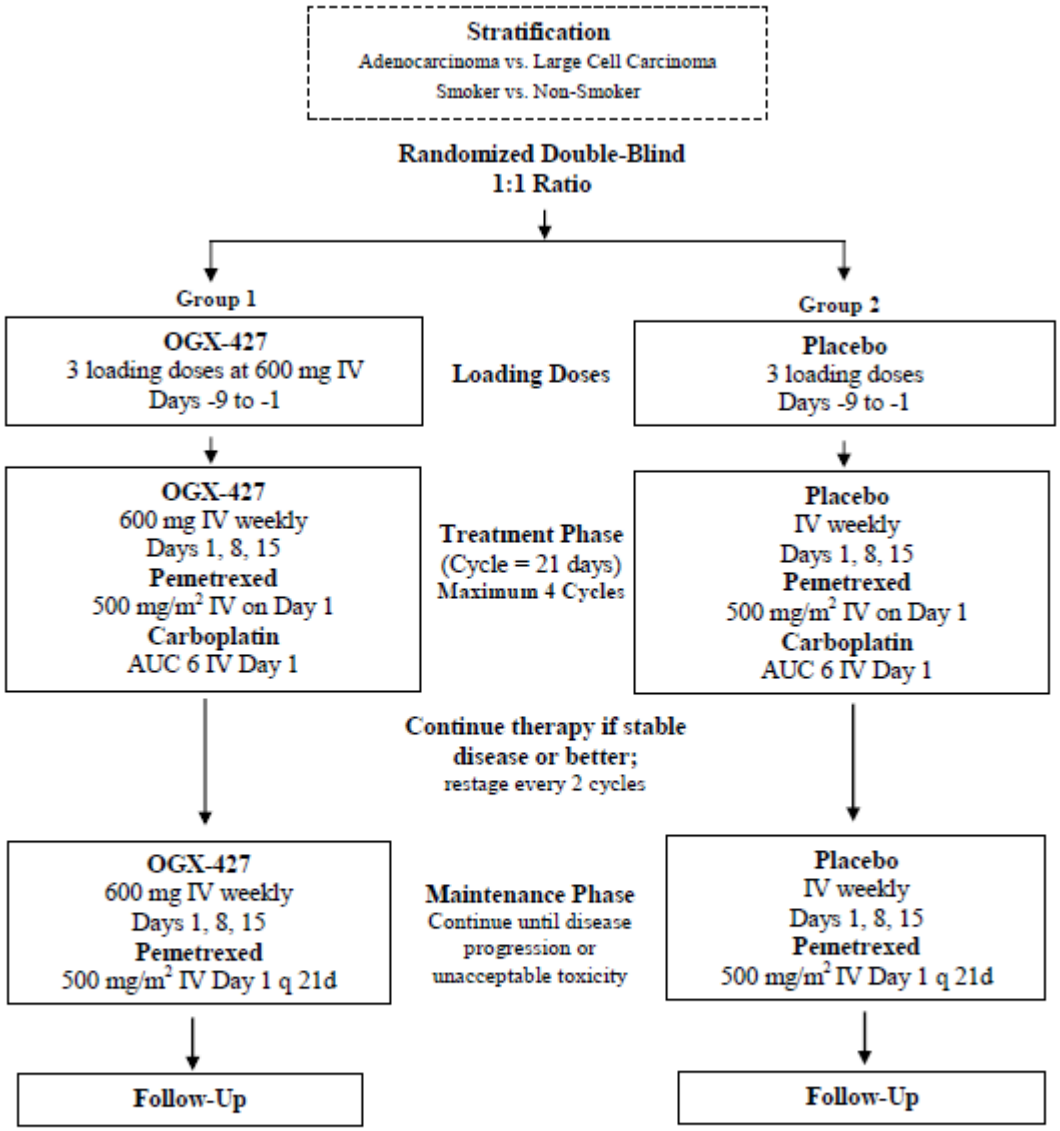
_____	_____	_____
Principal Investigator Name (Name Printed or Typed)	**Principal Investigator Signature**	**Date**

LUN 229 Synopsis

Title of Study:	Double-Blind Randomized Phase II Trial of Carboplatin and Pemetrexed with or without OGX-427 in Patients with Previously Untreated Stage IV Non-Squamous-Non-Small-Cell Lung Cancer (The Spruce Clinical Trial)	
SCRI Innovations Protocol Number:	LUN 229	
Sponsor:	SCRI Development Innovations	
Study Duration:	The duration of the study through the last patient treated including follow-up: 32 months	**Phase of Trial:** II
Number of Subjects:	The total number of patients expected to be accrued is 155.	
Objectives:	**Primary Objective** • To compare the progression-free survival (PFS) of OGX-427 plus carboplatin/pemetrexed therapy versus placebo plus carboplatin/pemetrexed in previously untreated patients with advanced non-squamous NSCLC. **Secondary Objectives** • To compare the objective response rate (ORR) in each treatment arm. • To compare overall survival (OS) in each treatment arm. • To evaluate safety **Exploratory Objectives** • Correlative analyses of serum levels of Hsp27. • Correlative analysis of treatment outcomes with specific biomarkers.	
Study Design:	This is a randomized, double-blind, placebo-controlled, Phase II study comparing pemetrexed and carboplatin plus OGX-427 followed by maintenance pemetrexed and OGX-427 versus pemetrexed and carboplatin plus placebo followed by maintenance pemetrexed and placebo in patients with previously untreated advanced non-squamous NSCLC. The patients, investigator, study team members, (except for the mixing pharmacist/nurse), and anyone involved with the conduct of the trial from the time of randomization until database lock for the primary endpoint analysis will be blinded to the identity of the treatment assignment (OGX-427 or placebo). The primary endpoint of the trial is PFS. A total of 155 patients will be randomized in a 1:1 ratio. Randomization will be stratified by histology (adenocarcinoma vs. large cell carcinoma) and smoking status (smoker vs. non-smoker) for the purpose of balance of enrollment and exploratory analysis.	

LUN 229 Synopsis (continued)

Study Drug(s), Dose, and Mode of Administration:	

LUN 229 Synopsis (continued)

Inclusion Criteria:	Patients must meet the following criteria in order to be included in the clinical study: 1. Histologic or cytologic diagnosis of advanced NSCLC, excluding squamous cell and small cell histology. Tumors with mixed NSCLC histologies are eligible, as long as the predominant histology is not squamous. If small-cell elements are present or not otherwise specified (NOS) histologically, the patient is not eligible. 2. Metastatic disease at the time of study entry (according to American Joint Committee on Cancer (AJCC) staging system, v7.0). 3. No prior systemic chemotherapy, immunotherapy, targeted therapy, or biological therapy for metastatic disease. Previous adjuvant or neoadjuvant therapy is allowed for Stage 1, II, or III disease as long as the interval from end of treatment until disease progression was >12 months. 4. No prior radiation therapy to the whole pelvis or to >25% of the total bone marrow area. Other radiation therapy must be completed at least 2 weeks prior to study entry. Must have recovered from acute adverse effects prior to study entry. 5. At least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Section 9). 6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1 (See Appendix A). 7. Baseline laboratory values as follows: • Absolute neutrophil count (ANC) ≥1500/μL • Hemoglobin (Hgb) ≥10 g/dL • Platelets ≥100,000/μL • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 x the upper limit of normal (ULN); 5 x ULN if known hepatic metastases. • Total bilirubin ≤1.5 x ULN, unless secondary to Gilbert's disease • Serum creatinine ≤1.5 x ULN. If creatinine is >1.5, calculate creatinine clearance ≥45 mL/min by the Cockcroft-Gault method: $$GFR = \frac{(140\text{-age}) \times (\text{weight/kg}) \times (0.85 \text{ if female})}{(72 \times \text{serum creatinine mg/dL})}$$ 8. Fertile male patients willing to use adequate contraceptive measures (see Appendix B). 9. Female patients who are not of child-bearing potential (see Appendix B), and fertile female patients of child-bearing potential who agree to use adequate contraceptive measures (see Appendix B), who are not breastfeeding, and who have a negative serum or urine pregnancy test within 72 hours prior to start of randomization. 10. Life expectancy ≥ 12 weeks. 11. Must be ≥18 years of age at the time of consent. 12. Willingness and ability to comply with trial and follow-up procedures. 13. Ability to understand the nature of this trial and give written informed consent

LUN 229 Synopsis (continued)

Exclusion Criteria:	Patients who meet any of the following criteria will be excluded from study entry: 1. Known ALK translocation and EGFR "activating" mutations where first-line treatment with targeted kinase inhibitor therapy is more appropriate. 2. Known central nervous system (CNS) disease other than neurologically stable, treated brain metastases – defined as metastasis having no evidence of progression or hemorrhage after treatment and no ongoing requirements for corticosteroids, (e.g., dexamethasone) for at least 2 weeks. 3. Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association [NYHA] ≥ Class 2 [See Appendix C]: • Unstable angina pectoris • Congestive heart failure • Acute myocardial infarction • Conduction abnormality not controlled with pacemaker or medication • Significant ventricular or supraventricular arrhythmias (Patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible). 4. Patients currently receiving therapeutic anticoagulation. 5. Pregnant or lactating women. 6. Any serious, active underlying medical condition that would impair the ability of the patient to receive study treatment, such as diabetes mellitus or infection. 7. Unable or unwilling to take folic acid or vitamin B12. 8. Active second malignancy (except non-melanomatous skin or superficial bladder cancer) defined as requiring current need for cancer therapy or at high risk of recurrence (>30%) during the study. 9. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 10. Inability or unwillingness to comply with trial and/or follow-up procedures outlined in the protocol.

LUN 229 Synopsis (continued)

Statistical Methodology:	Sample size considerations are based on progression-free survival (PFS) and follow-up considerations are based on overall survival (OS). The median PFS in the control group (carboplatin with pemetrexed plus placebo) is estimated to be approximately 5 months. A PFS target hazard ratio (HR) of 0.60, corresponding to a median PFS in the experimental group (carboplatin with pemetrexed plus OGX-427) of 8.3 months is hypothesized. The study will have 85% power to test this hypothesis using a one-sided log-rank at the 5% level of significance. Based on a uniform 15-month accrual period, a minimum of approximately 12 months follow-up period for PFS and a loss to follow-up/non-evaluability for PFS assessment rate of approximately 10% per year, a total of 155 subjects will be randomized in a 1:1 manner to achieve the targeted number of events in the scheduled PFS follow-up time. Sample size and power calculations were performed using PASS 2008 software. Descriptive statistics and statistical methods such as survival analysis and regression analysis will be used to assess the correlation of treatment outcomes with results from correlative testing.
Correlative Testing:	Blood samples will be collected from all patients and assessed for serum Hsp27 levels at baseline, prior to the initial loading dose, and during treatment. At these time points, approximately 7 mL of blood (red topped tube) will be collected for serum Hsp27. Hsp27 and AKT exist in complex with p38 MAPK and MK2 in the cytoplasm (Zheng et al. 2006). Studies have shown Hsp27 regulates AKT activation and promotes cell survival by scaffolding MK2 to the AKT signal (Zheng et al. 2006, Wu et al. 2007). The anti-tumor effect of Hsp27 inhibition might be associated with a decrease in AKT or other signaling pathway. Therefore, the status of PTEN loss and mutation status of a panel of genes are suggested to be explored to investigate whether specific biomarker status has predictive value for Hsp27 inhibition. Available archival tissues will be collected from patients and may be assessed for PTEN (protein expression by IHC) and mutations in a panel of genes including, but not limited to: ABL1, AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, FGFR4, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MET, MPL, MYC, NPM1, NRAS, PDGFRA, PIK3CA, PIK3R1, PTCH1, RUNX1, RET, SMO, STK11, and WT1.

LUN 229 Contact Information

SCRI Innovations Contact Information:	Sarah Cannon Research Institute Development Innovations 3322 West End Avenue, Suite 900 Nashville, TN 37203 877- MY-1-SCRI asksarah@scresearch.net
Study Chair:	David R. Spigel, MD Sarah Cannon Research Institute 3322 West End Avenue, Suite 900 Nashville, TN 37203 877-MY-1-SCRI asksarah@scresearch.net
Medical Monitor:	John D. Hainsworth, MD Sarah Cannon Research Institute 3322 West End Avenue , Suite 900 Nashville, TN 37203 877-MY-1-SCRI
Safety Dept. Phone # / Fax #:	615-329-7358 /866-807-4325
Regulatory Phone # / Fax #:	877-MY-1-SCRI /615-524-4518
SCRI Innovations Central Enrollment Email:	CANN.SCRIInnovationsEnr@scri-innovations.com
Central Pharmacy Fax #: **Central Pharmacy Email:**	866-325-9364 centralpharmacy@scresearch.net

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMP	comprehensive metabolic profile
CrCl	creatinine clearance
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group (Performance Status)
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HIPAA	Health Insurance Portability and Accountability Act
Hsp27	heat shock protein 27
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MRI	magnetic resonance imaging
NE	not evaluable
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancers
NYHA	New York Heart Association
OS	overall survival
PD	progressive disease
PET	positron-emission tomography
PFS	progression-free survival
PR	partial response

List of Abbreviations

RECIST	Response Evaluation Criteria in Solid Tumors
RR	response rate
SAE	serious adverse event
SCRI	Sarah Cannon Research Institute
SD	stable disease
ULN	upper limit of normal

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1 INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide (Pazdur et al 2004). Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of these cases. The majority of patients present with unresectable locally advanced or metastatic disease. Patients with advanced disease rarely survive 5 years, and over half die within the first year of diagnosis.

1.1 Background

Combination chemotherapy can extend survival, palliate symptoms of progressive disease, and improve the quality of life in patients with advanced NSCLC.

Pemetrexed is a novel, multi-targeted antifolate, antimetabolite agent that initially was approved by the US Food and Drug Administration (FDA) for the treatment of unresectable malignant pleural mesothelioma in combination with cisplatin after demonstrating superior response rates, time to progression (TTP), and survival compared with cisplatin alone (Vogelzang et al. 2003).

Scagliotti completed a multicenter, randomized, Phase III study of previously untreated locally advanced NSCLC patients, comparing pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) Day 1 every 21 days versus gemcitabine (1250 mg/m^2) Day 1 and Day 8 plus cisplatin (75 mg/m^2) Day 1 every 21 days. Overall survival (OS) with pemetrexed and cisplatin was statistically non-inferior to that achieved by gemcitabine and cisplatin (Scagliotti et al. 2008).

Pemetrexed and carboplatin were compared in a large Phase III study with standard gemcitabine and carboplatin as first-line chemotherapy for patients with advanced NSCLC (Gronberg et al. 2009). Of the 423 patients analyzed for toxicity the patients receiving pemetrexed and carboplatin had less hematologic toxicity and need for supportive care than the patients receiving gemcitabine and carboplatin.

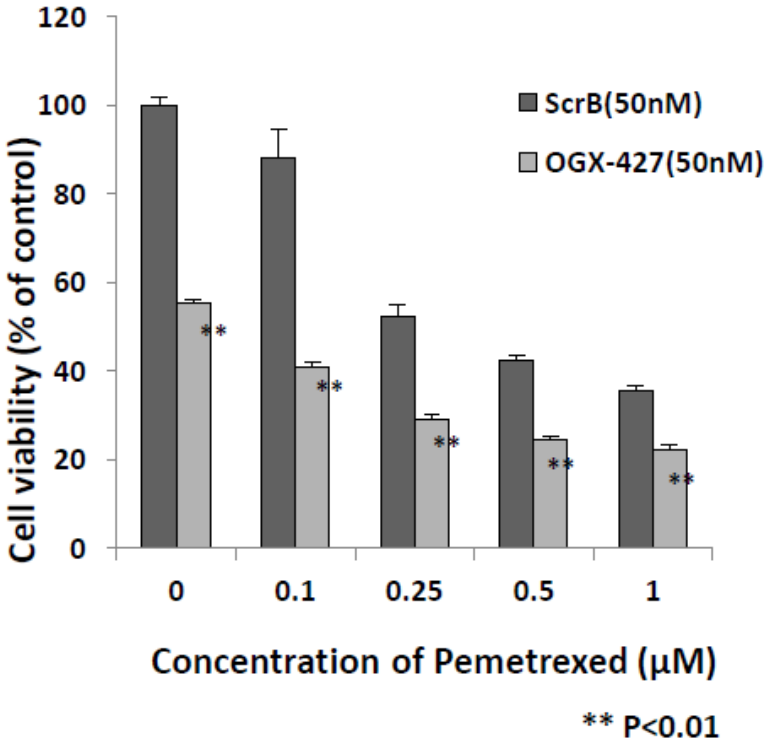
Maintenance treatment with pemetrexed following induction chemotherapy has been tested in a randomized, double-blind, placebo-controlled study (Ciuleanu et al. 2008). Patients in the trial received 1 of 6 standard regimens (gemcitabine, paclitaxel, or docetaxel) with cisplatin or carboplatin. Treatment selection was at the discretion of the investigator. Responders after 4 cycles (complete response [CR], partial response [PR], or stable disease [SD]) were randomly assigned maintenance therapy with either pemetrexed or best supportive care (BSC) plus placebo until progression. Improvement in the non-squamous NSCLC patient population was significant. OS was 14.4 months for the pemetrexed-treated patients and 9.4 months for the patents receiving placebo. In the same group, median progression-free survival (PFS) for pemetrexed versus placebo was 4.4 months versus 1.8 months.

1.1.1 OGX-427

OGX-427 is an antisense oligonucleotide (ASO) designed to bind to heat shock protein 27 (Hsp27) mRNA, resulting in the inhibition of the production of Hsp27 protein. Hsp27 is over-expressed in many cancers including prostate, breast, lung, and bladder. Increased

expression has been associated with inhibition of chemotherapy-induced apoptosis, increased cytoprotection and the development of treatment resistance. OGX-427 is an inhibitor of Hsp27 that effectively targets and down-regulates Hsp27 mRNA and has been shown to increase apoptosis, inhibit tumor growth, and sensitize cells to various chemotherapy regimens in a variety of malignancies. Gleave and his colleagues have shown enhanced antitumor effects with pemetrexed after treatment with OGX-427 in A549 cells (unpublished results see Figure 1).

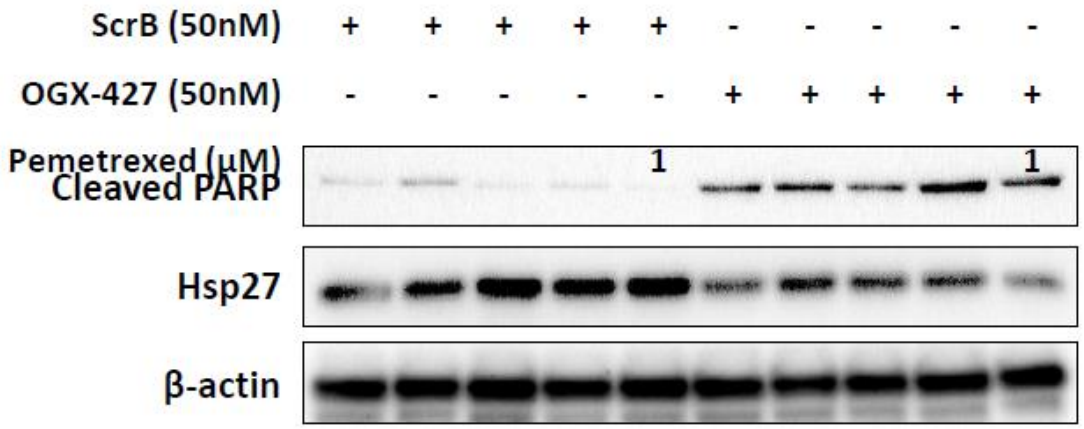
Figure 1: Enhanced Pemetrexed Effects After OGX-427 Treatment in A549 Cells



To evaluate cell cytotoxicity, A549 cells were treated with 50nM OGX-427 for 2 consecutive days and incubated with indicated concentration of Pemetrexed for 72 h ; 72 h later, cell viability was determined by crystal violet assay; ScrB = scrambled oligonucleotide

Increased apoptotic rates were also observed with pemetrexed after OGX-427 treatment in A549 Cells (Figure 2).

Figure 2: Pemetrexed Increases Apoptotic Rates After OGX-427 Treatment in A549 Cells



To evaluate cell apoptosis, A549 cells were treated with 50nM OGX-427 for 2 consecutive days and incubated with indicated concentration of Pemetrexed for 72 h ; 72 h later, total protein was extracted and analyzed by immunoblotting; ScrB = scrambled oligonucleotide.

Similar synergistic results have been observed with OGX-427 in combination with platinum (please refer to the OGX-427 Investigator Brochure for more detailed information).

1.2 Rationale for the Study

Modern doublet chemotherapy improves survival in patients with advanced NSCLC compared with supportive care alone. Recently, histology has emerged as a predictive marker for first-line treatment. Patients with non-squamous NSCLC treated with platinum/pemetrexed lived longer than patients treated with platinum/gemcitabine.

Moreover, pemetrexed resulted in a survival advantage in patients with non-squamous lung cancer when used as a maintenance therapy in the first-line setting compared with patients treated only at progression. Despite these recent advantages, overall survival for patients with advanced disease remains relatively poor.

OGX-427 is a 2'-methoxyethyl (MOE) oligonucleotide analogue which targets Hsp27. Hsp27 is a stress-activated ATP-independent cytoprotective chaperone which mediates treatment resistance in cancer. Preclinical models demonstrate that OGX-427 is a potent Hsp27 inhibitor across solid tumors. A phase I study of OGX-427 as monotherapy or in combination with docetaxel could not identify a maximum tolerated dose. There was a single dose-limiting toxicity of cerebral hemorrhage; however, infusion reactions were common. These reactions were largely low-grade and rarely (<1.5%) resulted in treatment modification. Several patients at varying dose levels had evidence of tumor shrinkage, including patients with NSCLC.

This randomized phase II study will compare the combination of carboplatin/pemetrexed with and without OGX-427 in patients with previously untreated advanced non-squamous NSCLC. The multicenter study will be conducted through the Sarah Cannon Research Institute network.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To compare the progression-free survival (PFS) of OGX-427 plus carboplatin/pemetrexed therapy versus placebo plus carboplatin/pemetrexed in previously untreated patients with advanced non-squamous NSCLC.

2.2 Secondary Objectives

- To compare the objective response rate (ORR) in each treatment arm.
- To compare overall survival (OS) in each treatment arm.
- To evaluate safety

2.3 Exploratory Objectives

- Correlative analyses of serum levels of Hsp27.
- Correlative analysis of treatment outcomes with specific biomarkers

3 TRIAL PATIENT POPULATION AND WITHDRAWAL

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the study:

1. Histologic or cytologic diagnosis of advanced NSCLC, excluding squamous cell and small cell histology. Tumors with mixed NSCLC histologies are eligible, as long as the predominant histology is not squamous. If small-cell elements are present or not otherwise specified (NOS) histologically, the patient is not eligible.
2. Metastatic disease at the time of study entry (according to American Joint Committee on Cancer (AJCC) staging system, v7.0).
3. No prior systemic chemotherapy, immunotherapy, targeted therapy, or biological therapy for metastatic disease. Previous adjuvant or neoadjuvant therapy for Stage I, II, or III disease is allowed as long as the interval from the end of treatment until disease progression was >12 months.
4. No prior radiation therapy to the whole pelvis or to ≥25% of the total bone marrow area. Other radiation therapy must be completed at least 2 weeks prior to study entry. Must have recovered from acute adverse effects prior to study entry.
5. At least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Section 9).
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1 (see Appendix A).

7. Baseline laboratory values as follows:
   - Absolute neutrophil count (ANC) ≥1500/μL
   - Hemoglobin (Hgb) ≥10 g/dL
   - Platelets ≥100,000/μL
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), ≤3.0 x the upper limit of normal (ULN); 5 x ULN if known hepatic metastases.
   - Total bilirubin ≤1.5 x ULN, unless secondary to Gilbert's disease
   - Serum creatinine ≤1.5 x ULN. If creatinine is >1.5, calculate creatinine clearance (CrCl) ≥45 mL/min by the Cockcroft-Gault method:

$$\text{GFR} = \frac{(140\text{-age}) \times (\text{weight/kg}) \times (0.85 \text{ if female})}{(72 \times \text{serum creatinine mg/dL})}$$

8. Fertile male patients willing to use adequate contraceptive measures (see Appendix B).
9. Female patients who are not of child-bearing potential (see Appendix B), and fertile female patients of child-bearing potential who agree to use adequate contraceptive measures (see Appendix B), who are not breastfeeding, and who have a negative serum or urine pregnancy test within 72 hours prior to start of randomization.
10. Life expectancy ≥ 12 weeks.
11. Must be ≥18 years of age at the time of consent.
12. Willingness and ability to comply with trial and follow-up procedures.
13. Ability to understand the nature of this trial and give written informed consent.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Known ALK translocation and EGFR "activating" mutations where first-line treatment with targeted tyrosine kinase inhibitor therapy is more appropriate.
2. Known central nervous system (CNS) disease other than neurologically stable, treated brain metastases – defined as metastasis having no evidence of progression or hemorrhage after treatment and no ongoing requirements for corticosteroids, (e.g., dexamethasone) for at least 2 weeks.
3. Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association [NYHA] ≥ Class 2 [see Appendix C]:
   - Unstable angina pectoris
   - Congestive heart failure
   - Acute myocardial infarction
   - Conduction abnormality not controlled with pacemaker or medication

- Significant ventricular or supraventricular arrhythmias (Patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible).

4. Patients currently receiving therapeutic anticoagulation.
5. Pregnant or lactating women.
6. Any serious, active underlying medical condition that would impair the ability of the patient to receive study treatment, such as diabetes mellitus or infection.
7. Unable or unwilling to take folic acid or vitamin B12.
8. Active second malignancy (except non-melanomatous skin or superficial bladder cancer) defined as requiring current need for cancer therapy or at high risk of recurrence (>30%) during the study.
9. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
10. Inability or unwillingness to comply with trial and/or follow-up procedures outlined in the protocol.

3.2.1 Discontinuation from Study Treatment

Patients will be discontinued from any phase of study treatment for one or more of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values requiring treatment discontinuation according to Section 6, Dose Modifications
- Unable to complete at least 3 cycles of at least one chemotherapy agent
- Patient requests to withdraw from the trial and discontinue treatment
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness or safety concerns which, per the investigator, prevent continuation of study treatment
- Non-compliance/lost to follow-up
- Global or severe deterioration of health status such that it requires discontinuation of protocol treatment without objective evidence of disease progression

After discontinuation from study treatment, patients must be followed for adverse events (AEs) for 30 calendar days after their last dose of study drug(s). All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for this decision in the patient's medical record and as a comment on the Case Report Form (CRF).

All patients who have Grade 3 or 4 laboratory abnormalities (Common Terminology Criteria for Adverse Events [CTCAE] v4.0 [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE]) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In

this case, the investigator must record his or her reasoning for making this decision in the patient's medical record and as a comment on the CRF.

3.2.2 Pregnancy

During the course of the study, all female patients of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix B) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period).

If an investigator suspects that a patient may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any study drug(s), and must be discontinued from the study.

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must notify the Sarah Cannon Research Institute (SCRI) Study Chair as soon as possible. If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form) should be completed and faxed to SCRI Innovations Safety Department. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 11.4.

4 STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts. Human protection committee approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be randomly assigned to treatment.

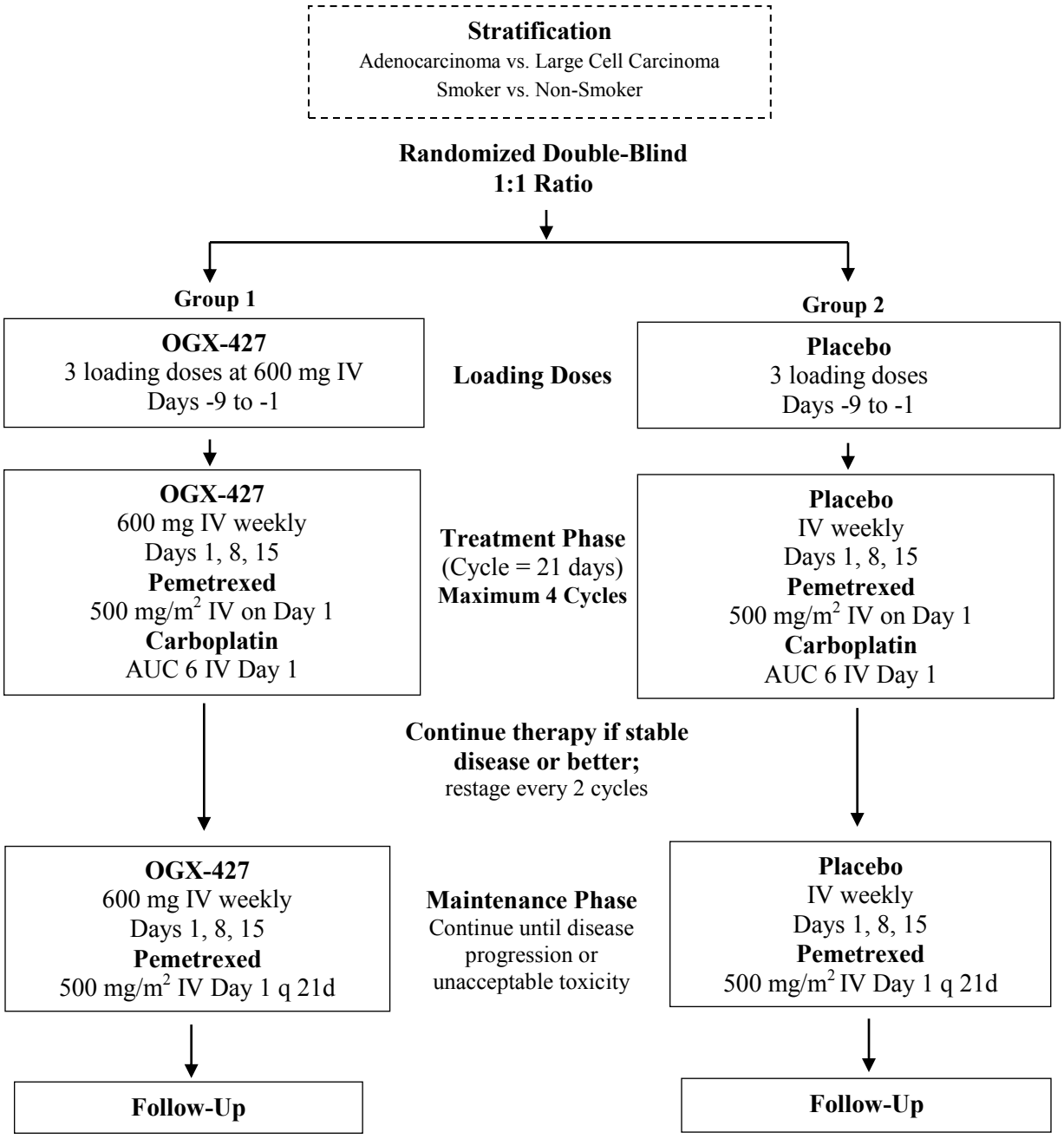
Registration and randomization must occur prior to the initiation of study therapy. For information regarding the study registration process, please refer to the study reference materials.

5 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, Phase II trial comparing pemetrexed and carboplatin plus OGX-427 followed by maintenance pemetrexed and OGX-427 versus pemetrexed and carboplatin plus placebo followed by maintenance pemetrexed and placebo in patients with previously untreated advanced non-squamous NSCLC. The patients, investigator, study team members, (except for the mixing pharmacist/nurse), and anyone involved with the conduct of the trial from the time of randomization until database lock for the primary endpoint analysis will be blinded to the identity of the treatment assignment (OGX-427 or placebo). The primary endpoint of the trial is PFS.

A total of 155 patients will be randomized in a 1:1 ratio. Randomization will be stratified by histology (adenocarcinoma vs. large cell carcinoma) and smoking status (smoker vs. non-smoker) for the purpose of balance of enrollment and exploratory analysis.

Figure 3 LUN 229 Treatment Schema



All patients will receive premedication for study drug (OGX-427 or placebo) with an antihistamine and an H2 antagonist, and a corticosteroid as described in Section 5.1. All patients will receive premedication for pemetrexed with folic acid, vitamin B_{12}, and dexamethasone as described in Table 1. Anti-emetics may be administered according to institutional standards.

5.1 Treatment Plan

Pre-medications for Study Drug (OGX-427/Placebo)

To reduce the potential of known potential allergic reactions occurring with OGX-427, patients will receive the following pre-medications 30-60 minutes prior to OGX-427/placebo administration during the loading doses and Cycle 1 (Days 1, 8 and 15).

- an antihistamine (diphenhydramine 25-50 mg or equivalent antihistamine)
- an H2 antagonist (ranitidine 50 mg or H2 antagonist equivalent)
- a corticosteroid (dexamethasone 8-12 mg or corticosteroid equivalent)

If the patient has not manifested signs or symptoms of an infusion reaction during the loading doses and Cycle 1, the patient may be treated in subsequent cycles without some or all of the pre-medications. However, should Grade 2 or greater reactions occur, the patient should resume pre-medications, including dexamethasone, prior to study drug for the duration of treatment.

Table 1. Premedications for Pemetrexed/Carboplatin

Patients will receive premedications for pemetrexed/carboplatin as shown in Table 1.

Premedications	**Dosing**	
Folic acid	350-1000 µg PO daily	Beginning ≤1 week before the first infusion of pemetrexed and continuing until 3 weeks after discontinuation of pemetrexed
Vitamin B_{12}	1000 mcg IM Q9W	Beginning ≤1 week before the first infusion of pemetrexed and continuing until 3 weeks after discontinuation of pemetrexed
Dexamethasone	8-12 mg IV Day 1 of each Cycle (Recommended)	May substitute institutional equivalent NOTE: If equivalent dexamethasone has been administered on Day 1 of a cycle prior to the study drug, additional dexamethasone prior to pemetrexed/carboplatin is at the discretion of the treating investigator.
Prophylactic Anti-emetics	Administered per local institutional guidelines.	

Study Drug - OGX-427 (or Placebo) Loading Doses:

Treatment will be initiated within 5 days from randomization with a Loading Dose Period (Day -9 to Day -1) followed by 21-day (3 week) study treatment cycles.

Three separate administrations of study drug will be given during the 9-day Loading Dose Period. The 3 loading doses (600 mg OGX-427 or placebo) must be administered with at least one "non-treatment" day between each dose (i.e. every other day). This 9-day period for the loading doses allows for variations in the treatment schedule due to holidays and clinic schedules. There must also be a minimum of 1 and no more than 7 days between the third loading dose and Cycle 1, Day 1.

Study Treatment Phase:

Patients will receive the study drug, 600 mg OGX-427 or placebo, prior to the administration of pemetrexed and carboplatin administration on Day 1 of each cycle. A maximum of 4 cycles will be given. Study drug will also be administered on Day 8 and Day 15 during each cycle (i.e., weekly).

Study Drug:

OGX-427 or placebo will be administered intravenously, after preparation in D5W. OGX-427 or placebo should be added to 250 mL D5W as close to the time of administration as possible. The dose will be administered intravenously as an infusion over approximately 2 hours using either a peripheral or central indwelling catheter. Refer to Section 8.1 for preparation and administration instructions for OGX-427 or placebo.

Pemetrexed: 500 mg/m^2 IV Day 1 q 21d

Infuse over approximately 10 minutes or according to institutional standards within approximately 30 minutes after the end of the Study Drug infusion

Carboplatin: Area Under the Curve (AUC) 6 IV Day 1 q 21d

Carboplatin, at a dose calculated to produce an AUC of 6 will be administered by intravenous infusion according to institutional standards beginning after the end of the pemetrexed infusion.

The carboplatin dose will be calculated using the Calvert Formula based on the patient's glomerular filtration rate (GFR) which is estimated by using the CrCl.

Calvert Formula: Carboplatin dose (mg) = target AUC x (GFR + 25)

The Food and Drug Administration (FDA) has recommended that physicians consider capping the dose of carboplatin for the desired exposure (AUC) to avoid potential toxicity due to overdosing for all laboratories using the IDMS-derived serum creatinine measurements. Therefore the maximum dose of carboplatin should be based on a CrCl no greater than 125 mL/min for patients with normal renal function. In these, carboplatin can be safely dosed according to the instructions in the drug's labeling. Refer to US FDA, Center for Drug Evaluation and Research website:

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm for more specific guidelines.

Cockcroft-Gault Formula:

$$\text{CrCl (GFR)} = \frac{[(140 - \text{age}) \times (\text{wt in kg})] \times (0.85 \text{ if female})}{(72 \times \text{serum creatinine [mg/dL]})}$$

5.2 Restaging During the Treatment Phase

Restaging by CT scans per RECIST version 1.1 (see Appendix E) will occur after Cycle 2 and Cycle 4 (see Section 7.5). A maximum of 4 treatment cycles will be given. If there is no evidence of progressive disease or irreversible toxicity, patients will begin weekly maintenance therapy as described in Section 5.3.

5.3 Maintenance Phase

Patients who have been discontinued from the Study Treatment Phase for disease progression, unacceptable toxicity, voluntarily withdrew from further treatment in the study or were removed from the Study Treatment Phase before receiving a minimum of 3 cycles containing at least one chemotherapy agent are **not** eligible for the Maintenance Phase.

Patients who have objective response or stable disease after four cycles of therapy (minimum of three cycles) will then move to the Maintenance Phase of the trial. Patients will receive pre-medications with folic acid, vitamin B12 and dexamethasone as described in Table 1.

During maintenance therapy patients will receive pemetrexed 500 mg/m^2 IV and Study Drug on Day 1 every 21 days followed by Study Drug on Days 8 and 15 of every cycle.

There will be no crossover of drug treatments.

During the Maintenance Phase, patients will be reevaluated by CT scans (per RECIST version 1.1; see Section 9) every 6 weeks (after every 2 treatment cycles). Patients will be eligible to continue maintenance treatment as long as they are benefiting and have no evidence of disease progression, and do not meet any criteria for discontinuation or withdrawal (see Section 3.2.1).

5.3.1 Correlative Testing

Blood samples will be collected from all patients and assessed for serum Hsp27 levels at baseline, prior to the initial loading dose, and during treatment. At these time points, approximately 7 mL of blood (red topped tube) will be collected for serum Hsp27.

Hsp27 and AKT exist in complex with p38 MAPK and MK2 in the cytoplasm (Zheng et al. 2006). Studies have shown Hsp27 regulates AKT activation and promotes cell survival by scaffolding MK2 to the AKT signal complex (Zheng et al. 2006, Wu et al. 2007). The anti-tumor effect of Hsp27 inhibition might be associated with a decrease in AKT or other signaling pathway. Therefore, the status of PTEN loss and mutation status of a panel of genes are suggested to be explored to investigate whether specific biomarker status has predictive value for Hsp27 inhibition.

Available archival tissues will be collected from patients and may be assessed for PTEN (protein expression by IHC) and mutations in a panel of genes including, but not limited to: ABL1, AKT1, ALK, B-Raf, CTNNB1, DDR2, EGFR, HER2, FGFR1, FGFR2, FGFR3, FGFR4, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KIT, K-Ras, MEK1, c-Met, MPL, Myc, NPM1, NRas, PDGFRA, PI3KCA, PI3KR1, RUNX1, SMO, PTCH1, LKB-1, RET, and WT1.

A paraffin-embedded tumor tissue block (from the primary tumor or metastasis) obtained at diagnosis may be used. In the absence of paraffin-embedded tissue, 15 unstained paraffin-embedded tumor slides are acceptable.

5.4 Concomitant Medications

Patients will be instructed to notify the investigator of any additional medications taken (including over-the-counter products) during the course of the study.

The use of granulocyte colony-stimulating factor (G-CSF) should follow the American Society for Clinical Oncology guidelines. All other supportive care may be administered as per institutional standard protocol.

5.4.1 Palliative Radiotherapy

Patients may receive palliative therapy during the trial only for local pain control, and only if in the opinion of the treating Investigator the patient does not have progressive disease. The radiation field cannot encompass a target lesion. Radiation to a target lesion is considered progressive disease and the patient should be removed from study treatment.

5.4.2 Leucovorin

Folic acid and vitamin B_{12} supplementation has significantly reduced the number of episodes of grade 4 hematologic and grade 3 or 4 non-hematologic toxicities associated with pemetrexed therapy; a need for leucovorin as a rescue agent is not anticipated. However, this section provides information should rescue be necessary.

In clinical trials, leucovorin was permitted for grade 4 leukopenia that lasted ≥3 days, grade 4 neutropenia that lasted ≥3 days, and was immediately permitted for grade 4 thrombocytopenia, bleeding associated with grade 3 thrombocytopenia, or grade 3 or grade 4 mucositis. The doses and schedules of leucovorin recommended for IV use are 100 mg/m^2 IV once, followed by 50 mg/m^2 leucovorin IV every 6 hours until recovery of counts. However, institutional standards may be followed.

5.4.3 Medications and Non-Drugs Prohibited During the Trial

At each visit, the investigator will ask the patient about any new medications he/she has taken after the start of study treatment.

All concomitant medications/significant non-drug therapies taken ≤30 days prior to start and after start of study treatment, including physical therapy and blood transfusions, should be recorded.

The following restrictions apply during the entire duration of the trial:

- No other investigational therapy should be given to patients.
- Concomitant cancer treatment (e.g., biologic, hormonal therapy, immunotherapy, chemotherapy, and radiation therapy for disease progression) is prohibited. If such treatment is required, then the patient must first be withdrawn from the trial.
- No chronic treatment with systemic steroids (at a dose equivalent of greater than 20 mg prednisone per day) other than those used for premedication per protocol or treatment with immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- Patients requiring therapeutic warfarin or coumarin-derivative anticoagulants will be monitored with INR and Prothrombin Time as clinically indicated.
- Caution should be used when administering nonsteroidal anti-inflammatory drugs (NSAIDs) concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance 45-79 mL/min). NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of 2 days before, the day of, and 2 days following administration of pemetrexed. NOTE: No dose adjustment of pemetrexed is needed with concomitant NSAIDs in patients with normal renal function.

  In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt NSAID dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myeloid, renal, and gastrointestinal toxicity.

  Ibuprofen (400 mg four times a day) can decrease the clearance of pemetrexed; however, it can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥80 mL/min).

5.5 Treatment Assignment Unblinding Procedures

There is no intention to routinely unblind individual patients at any time. Individual requests for urgent safety unblinding require the approval of the Medical Monitor.

There also may be instances where unblinding of a patient(s) may be required for a safety review at the request of the SCRI Innovations Medical Monitor or DSM or for Regulatory Authority reporting requirements.

After all patients have completed protocol treatment and the database has been locked, the trial will be unblinded for analysis of the safety and efficacy outcomes.

6 DOSE MODIFICATIONS

All toxicities will be graded utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE). If toxicity occurs, the toxicity will be graded, and appropriate supportive care treatment will be administered to decrease the signs and

symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. A maximum of two dose reductions for the Study Drug or either chemotherapy will be allowed. Patients requiring >2 dose reductions will be discontinued from the offending study drug/chemotherapy but will be allowed to continue on other agent(s) if appropriate.

Doses of **pemetrexed** and **carboplatin** as well as Study Drug if indicated will be modified based on hematologic and non-hematologic toxicity. If dose reductions are necessary they will be permanent for the remainder of the treatment. Doses will be adjusted according to the dose modification tables that follow. Any patient requiring a toxicity-related dose delay of more than 21 days from the intended day of the next scheduled dose must be discontinued from the offending agent(s).

Table 2. Pemetrexed Dose Level Modifications

Dose Level	Pemetrexed (IV mg/m^2)
0 (starting dose)	500
-1	400
-2	300

Table 3. Carboplatin Dose Level Modifications

Dose Level	Carboplatin (AUC)
0 (starting dose)	6
-1	5
-2	4

Table 4. OGX-427 Dose Level Modifications

Dose Level	OGX-427(IV mg)
0	600 mg
-1	500 mg
-2	400 mg

To maintain study blinding, the volume for OGX-427/placebo will be adjusted to ~ 290 mL for each administration.

6.1 Hematologic Toxicity

Blood counts will be obtained at the beginning of each cycle. To start a new treatment cycle, the patient must have the following blood counts: ANC ≥1500/μL and platelet count ≥100,000/μL. Hematologic dose modifications apply only to Day 1 values of each cycle. Dose reductions are not based on nadirs occurring during the previous treatment cycle.

Dose level modifications for pemetrexed, carboplatin, and Study Drug due to hematologic toxicity are shown in Table 5. For toxicities that lead to a dose reduction, the dose will not be re-escalated during subsequent cycles. If hematologic parameters do not recover within ≤3 weeks (21 days), the patient should be removed from the Study Treatment Phase and start the Maintenance Phase if appropriate (see Section 5.3).

Grade 3 and 4 anemia should be treated along ASCO and Institutional Guidelines.

Table 5. Day 1 Hematologic Dose Modifications

Blood Counts	Pemetrexed[a]	Carboplatin[a]	Study Drug
ANC ≥1500/μL; Platelets ≥100,000/μL	No dose modification	No dose modification	No dose modification
ANC <1500/μL and/or; Platelets <100,000/μL	Delay dose[b] and resume with a reduction of 1 dose level (Table 2)	Delay dose[b] and resume with a reduction of 1 dose level (see Table 3)	Delay dose[b] and resume with a reduction of 1 dose level only for the second or subsequent occurrence (see Table 4)
Grade 3 neutropenic fever (ANC <1000/μL + Temperature ≥101°F (38.5°C)) or neutropenic infection	Treat neutropenic fever or infection according to institutional guidelines. Resume with reduction of 1 dose level (see Table 2)	Resume with reduction of 1 dose level. Consider G-CSF (see Table 3)	Delay dose[b] and resume with a reduction of 1 dose level
Documented infection with Grade 3 neutropenia (ANC <1000/μL) Grade 4 neutropenia (ANC <1000/μL >7 days) Grade 4 thrombocytopenia (platelet count <25 x 10^9/L >7 days	With recurrence of any of these toxicities, the patient should be removed from study treatment.	With recurrence of any of these toxicities, the patient should be removed from study treatment.	With recurrence of any of these toxicities, the patient should be removed from study treatment.
Grade 4 febrile neutropenia or grade 4 infection with neutropenia (both defined as septic shock). Thrombocytopenic hemorrhage (gross not occult bleeding) associated with a platelet count <50 x 10^9/L	Remove patient from study treatment and follow for disease progression	Remove patient from study treatment and follow for disease progression	Remove patient from study treatment and follow for disease progression

[a] No more than two dose reductions will be allowed for any patient. Patients requiring additional dose modifications due to toxicity will discontinue protocol treatment.

[b] Hold chemotherapy cycle until hematologic parameters return to adequate levels (i.e., ANC ≥1500/μL, platelets ≥100,000/μL). If hematologic parameters have not recovered within 21 days (3 weeks), the patient will be removed from the study treatment.

Note: Hematologic dose modifications apply only to Day 1 values of each cycle. Dose reductions are not based on nadirs occurring during the previous treatment cycle.

6.2 Non-Hematologic Toxicity Dose Modifications

Dose modifications for non-hematologic toxicities should be based on toxicities occurring during the previous cycle. Most dose modifications below, but not all, are for both chemotherapies. If grade 3 or 4 non-hematologic toxicity (other than nausea, vomiting, fatigue, malaise, anorexia, lethargy, or alopecia) occurs, treatment with pemetrexed, carboplatin, and possibly Study Drug (see below) should be held, and should be resumed at a one level dose reduction (see Table 2 and Table 3) once toxicity recovers to ≤ grade 1. If the toxicity is clearly attributable to one drug, then dose reduction of only that drug is necessary. For example, if the toxicity is known to occur with only one of the chemotherapeutic agents (e.g. neurotoxicity with carboplatin but not pemetrexed or diarrhea with pemetrexed but not carboplatin) the patient may remain on study treatment and only the offending chemotherapy will be held, dose adjusted, or discontinued. Although there is little evidence that OGX-427 increases toxicity above that of chemotherapeutic agent(s) it is administered with, except for infusion reactions, whether Study Drug is held, adjusted, or discontinued is up to the discretion of the treating Investigator. For toxicities that lead to a dose reduction, the dose will not be re-escalated during subsequent cycles. Any patient who develops grade 3 or 4 toxicity (in the Study Treatment Phase or the Maintenance Phase) that does not resolve to ≤ grade 1 within 3 weeks should be removed from the study treatment.

Table 6. Non-Hematologic Toxicity Dose Modifications

NCI CTCAE Grade	Pemetrexed Dose	Carboplatin Dose	Study Drug
Grade 0, 1, or 2 (except neurotoxicity)	No modification	No modification	No modification
Grade 3[b,c, d, e] (except transaminase elevation)	Hold[a]	Hold[a]	Hold[a]
Grade 4[b, e] Toxicity resolves to grade ≤1	Resume with a one level dose reduction	Resume with a one level dose reduction	Resume with a one level dose reduction
Second repeat incidence of Grade 3 or 4 toxicity (except nausea, vomiting, fatigue/malaise/ lethargy, anorexia, and alopecia)	Discontinue treatment	Discontinue treatment	Discontinue treatment
Grade 2 Creatinine Clearance (calculated by Cockcroft-Gault method)	Hold	No modification	No modification
Grade 3 Creatinine Clearance (calculated by Cockcroft-Gault method)	Hold[a]	Hold[a]	Hold
Grade 4 Creatinine Clearance (calculated by Cockcroft-Gault method)	Once toxicity resolves to Grade ≤1 resume with a one level dose reduction	Once toxicity resolves to Grade ≤1 resume with a one level dose reduction	Once toxicity resolves to Grade ≤1 resume with a one level dose reduction
Mucositis Grade 3 or 4	Hold[a]	Hold[a]	Hold
Mucositis resolves to grade ≤1	Resume with a one level dose reduction	No modification	No modification
Transaminase Elevation Grade 1-3	No modification	No modification	No modification
Transaminase Elevation Grade 4	Hold[a]	Hold[a]	Hold[a]
Neurotoxicity Grade 1 or 2	No modification	Reduce with a two level dose reduction	No modification
Neurotoxicity Grade 3 or 4	Discontinue treatment	Discontinue treatment	Discontinue treatment
Diarrhea Grade 3 or 4 or requiring hospitalization	Hold[a]	Hold[a]	Hold
Toxicity resolves to grade ≤1	Resume with a one level dose reduction	No modification	No modification

[a] Both chemotherapy agents should be held until toxicity resolves to ≤ grade 1. Any patients who develop irreversible grade 3/4 non-hematologic toxicity, or toxicity that does not resolve to ≤ grade 1 within 3 weeks, should be removed from the study treatment. No more than 2 dose reductions are allowed for either chemotherapy agent.

[b] Dose reduction for nausea and vomiting should be made only if grade 3 or grade 4 toxicity occurs in spite of maximum antiemetics.

[c] No dose reduction is needed for grade 1-3 transaminase elevations.

[d] For a Grade 3 pulmonary embolism, the dose should be held but the subsequent doses do not have to be reduced one dose level, at the Investigator's discretion.

[e] Patients who manifest a Grade 3 electrolyte value(s) i.e., hypokalemia, do not require a dose reduction once the electrolyte issue is resolved. Patients who manifest a Grade 4 electrolyte value(s) do not have to be removed from protocol for a Grade 4 electrolyte value, at the Investigator's discretion; Example: Grade 4 elevated glucose in a patient with diabetes mellitus.

6.2.1 Specific Non-Hematologic Toxicities

6.2.1.1 Diarrhea

In the event of grade 3 or 4 diarrhea, the following supportive measures are recommended: hydration, octreotide, and anti-diarrheals.

If diarrhea is severe (i.e., requiring IV rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for IV hydration and correction of electrolyte imbalances.

6.2.1.2 Febrile Neutropenia

Patients experiencing febrile neutropenia with significant symptoms should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Patients with febrile neutropenia without symptoms should be managed according to standard guidelines.

6.2.1.3 Clinically Significant Effusions

For patients who develop or have baseline clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) before or during initiation of pemetrexed therapy, consideration should be given to draining the effusion prior to dosing.

6.2.1.4 Motor Neuropathy or Muscle Weakness

Any onset of > grade 2 motor neuropathy or > grade 2 muscle weakness should be evaluated by an electromyogram (EMG) to rule out the possibility of chronic inflammatory demyelinating polyneuropathy (CIDP). With a diagnosis of CIDP the patient should be discontinued from study treatment.

6.3 Dose Modifications for Infusion Reactions

Infusion reactions (e.g. rash, urticaria, erythema, pruritus, bronchospasm, and hypotension) can occur with the agents used in this study. There is increased risk of a reaction with carboplatin. Carboplatin must be discontinued in patients experiencing a grade 3 or 4 infusion reaction during treatment.

To identify the grade of a reaction, refer to the list below adapted for the General Disorders and Administration Site Conditions section of the NCI CTCAE Version 4.0:

- Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated.
- Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids indicated for ≤24 hours).
- Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic mediation and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae. Note: any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.
- Grade 4: Life-threatening consequences; urgent intervention indicated.

If any of the agents are discontinued due to an infusion reaction, the other agent(s) may be continued.

In the event of an infusion reaction, obtain vital signs, follow the institutional guidelines of each site and the recommendations shown in the tables below for OGX-427/placebo infusion reactions based on the grade of the reaction.

Table 7. Dose Modifications for Infusion Reaction for OGX-427/Placebo

Toxicity	Dose Modification
Any Grade 1 infusion reaction	Slow the rate of infusion of the drug until resolution of symptoms, then resume at the planned infusion rate.
Grade 2 or 3 infusion reaction in a patient not on steroid prophylaxis	Stop the infusion. Give dexamethasone 8 mg IV, diphenhydramine 50 mg IV, and/or an H2 antagonist (e.g. Ranitidine 50 mg IV) after consultation with the attendant physician. Resume after recovery of symptoms at a slower rate, and then increase incrementally toward the initial rate. **Resume premedication regimen to include dexamethasone 8 mg, diphenhydramine 50 mg, and/or an H2 antagonist.**
Grade 2 or 3 infusion reaction in the presence of steroid prophylaxis (after initial loading doses)	Stop the infusion. Give dexamethasone 8 mg IV, diphenhydramine 50 mg IV, and/or an H2 antagonist (e.g. Ranitidine 50 mg IV) after consultation with the attendant physician. Resume after recovery of symptoms at a slower rate, and then increase incrementally toward the initial rate. **Reduce the OGX-427/placebo by one dose level for all subsequent doses.**
Grade 4 infusion reaction	Stop the infusion. Discontinue OGX-427/placebo.

*There will be no dose reductions of OGX-427/placebo during the Loading Dose period. Per protocol, all patients are given a lower dose of OGX-427/placebo and receive maximal prophylactic medication during the loading dose period in attempt to decrease the incidence and severity of any infusion reaction. Grade 3 reactions have been uncommon in other OGX-427 trials.

7 TRIAL ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the trial center on the days specified within this protocol. The baseline medical history, physical examination, ECOG PS, complete blood counts (CBC) with 3-part differential and platelets, and comprehensive metabolic profile (CMP), should be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours prior to the initiation of treatment they do not have to be repeated. Scans should be performed ≤ 4 weeks prior to initiation of treatment.

7.2 Baseline Trial Assessments

- Informed consent form prior to any other study related procedures
- Medical history and demographics
- Smoking history
- Physical examination including measurements of height (first visit) and weight
- Vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature)
- ECOG PS (see Appendix A)
- Concomitant medication review
- CBC including 3-part differential and platelets
- CMP (See Section 7.9)
- 7 mL blood (red top tube) for serum Hsp27
- Serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)
- Archived tumor tissue (See Section 5.3.1)
- Electrocardiogram (ECG) (repeat if clinically indicated)
- Tumor Evaluation
    - CT Scan of Chest to include adrenal glands (CT Scan of Abdomen and Pelvis required if adrenal glands are not included on CT Scan of Chest)
    - PET Scan or Bone scan
    - CT Scan Head or MRI Brain

7.3 Study Treatment Assessments

7.3.1 OGX-427 (or Placebo) Loading Dose Period Assessments

- Vital signs pre-dosing (resting heart rate, blood pressure, respiratory rate, oral temperature)
- AE assessment
- Concomitant medication review
- 7 mL blood (red top tube) for serum Hsp27 (prior to first loading dose)

7.4 Treatment Phase Assessments

7.4.1 Cycle 1 Day 1

- Physical examination including measurement of weight and vital signs
- ECOG PS (see Appendix A)
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP (See Section 7.9)
- 7 mL blood (red top tube) for serum Hsp27

7.4.2 Cycle 1 Days 8 and 15 (±72 hours)

- Vital signs pre-dosing
- CBC, including 3-part differential and platelets (Day 8 and Day 15)
- AE assessment (Day 8 and Day 15)
- Concomitant medication review
- CMP (see Section 7.9) (Day 8 and Day 15)

7.4.3 Cycles 2 – 4, Day 1 (±72 hours)

- Physical examination including measurement of weight and vital signs pre-dosing
- ECOG PS (see Appendix A)
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP (See Section 7.9)
- 7 mL blood (red top tube) for serum Hsp27

7.4.4 Cycles 2 – 4 Days 8 and 15 (±72 hours)

- Vital signs pre-dosing
- CBC, including 3-part differential and platelets
- AE assessment
- Concomitant medication review

7.5 Every 2 Cycles (6 Weeks)

Patients will be evaluated for response to treatment after every 2 cycles of treatment (end of Cycles 2 and 4). The following assessments will be performed if abnormal at baseline or clinically indicated:

- Tumor Evaluation

- CT Scan of Chest with adrenal glands included. (CT Scan of Abdomen and Pelvis required if adrenal glands are not included on CT Scan of Chest)

7.6 Maintenance Treatment Assessments

7.6.1 Day 1 Every 21 Days (±72 hours)

- Physical examination including measurement of weight and vital signs pre-dosing
- ECOG PS (see Appendix A)
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP (See Section 7.9)
- 7 mL blood (red top tube) for serum Hsp27

7.6.2 Maintenance Days 8 and 15 (±72 hours)

- Vital signs pre-dosing
- CBC, including 3-part differential and platelets
- AE assessment
- Concomitant medication review

7.6.3 Every 2 Cycles (6 Weeks) During Maintenance (±7 days)

Patients will be re-evaluated for response to treatment after every 2 cycles during the maintenance portion. The following assessments will be performed if abnormal at baseline or clinically indicated:

- Tumor Evaluation
  - CT Scan of Chest with adrenal glands included. (CT Scan of Abdomen and Pelvis required if adrenal glands are not included on CT Scan of Chest)

7.7 End of Study Treatment

Subjects will return to the study center within 30 days after treatment ends due to progressive disease, or discontinuation from trial treatment due to unacceptable toxicity or a decision to discontinue study treatment by the subject or the study physician.

- Physical examination including measurement of weight and vital signs
- ECOG PS (see Appendix A)
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP (See Section 7.9)
- 7 mL blood (red top tube) for serum Hsp27
- Tumor Evaluation

- CT Scan of Chest with adrenal glands included if not performed within last 30 days. (CT Scan of Abdomen and Pelvis required if adrenal glands are not included on CT Scan of Chest)

7.8 Follow-Up

7.8.1 Progression-Free Survival Follow-Up

Patients who discontinue trial treatment prior to the occurrence of disease progression will be followed every 6 weeks from the date of last dose of study drug until disease progression or for up to 2 years whichever comes first. Assessments at these visits will be performed as described in Appendix D. Any subsequent cancer therapy will be documented.

7.8.2 Survival Follow-Up

After disease progression is documented, subjects will be followed every 2 months for survival (e.g., date and cause of death) for up to 2 years or death, whichever comes first. Subjects may be contacted during outpatient visits or by telephone (contact with family member acceptable). Any subsequent cancer therapy will be documented.

7.9 Comprehensive Metabolic Profile Assessments

The CMP panel can sometimes vary by institution. The following laboratory tests should be performed for each subject for assessment of CMP:

- glucose
- blood urea nitrogen (BUN)
- creatinine
- sodium
- potassium
- chloride
- calcium
- carbon dioxide (CO2)
- alkaline phosphatase (ALP)
- AST
- ALT
- total bilirubin
- total protein
- albumin

8 DRUG FORMULATION, AVAILABILITY, ADMINISTRATION AND TOXICITY INFORMATION

8.1 Study Drug (OGX-427 or Placebo)

This is a blinded study. Access to treatment assignment codes will be restricted to one or more mixing pharmacists/nurses who will be responsible for maintaining assignment records and all Study Drug (OGX-427 or Placebo) preparation.

OGX-427 will be provided by OncoGenex Technologies, Inc. Placebo will be D5W supplied by the site pharmacy. Trial sites will obtain OGX-427 per instructions provided by SCRI Innovations to the participating sites. Once OGX-427 is shipped to a site, it may not be shipped or shared with another site or subject.

8.1.1 Labeling, Packaging and Supply

All clinical trial material will be labeled in accordance with local and federal regulations, stipulating that the product is for investigational use only. Vials of OGX-427 must be stored in a secure, temperature monitored refrigerator, at a temperature of 2 - 8° C (36-46° F) until the time of use. Do not freeze. The drug substance and active ingredient of OGX-427 is an antisense oligonucleotide (ASO). Refer to the Investigator's Brochure for complete information.

OGX-427 dosing solutions will be administered intravenously preferably using an infusion pump. Once mixed for administration, it is recommended that the OGX-427 dosing solution be administered within 24 hours if kept at room temperature or refrigerated (2-8° C, 36-46° F). Investigational drug accountability records will be maintained documenting the utilization of the study drug at the clinical site.

Placebo will be D5W supplied by the site pharmacy. An additional 40 mL of D5W will also be added to 250 mL of D5W so that the volume of placebo will be the same as the volume of OGX-427 at each dose level to maintain the blind.

8.1.2 Preparation and Administration of Study Drug

The OGX-427 drug dilution procedure should be performed according to the instructions below and following proper aseptic technique:

OGX-427 should be stored between 2 - 8° C (36 – 46°F) prior to use.

Once dose instructions have been received from the site Investigator, remove OGX-427 from the refrigerator and inspect the vials for particulate matter. Vials containing particulate matter should not be used.

Using proper aseptic technique withdraw the correct amount of OGX-427 from each vial using a syringe and a needle.

To prepare Study Drug, begin with 250 mL of D5W, then add OGX-427, and additional D5W if required to the intravenous D5W solution, as shown in the table below. For placebo add 40 mL of D5W to 250 mL of D5W.

Dose Period	Dosage	# of vials	Volume of OGX-427	Volume of D5W
Loading Dose	600 mg	3	24 mL	16 mL
Treatment Cycles	600 mg	3	24 mL	16 mL
Maintenance	600 mg	3	24 mL	16 mL

Attach the intravenous tubing to the bag and prime the IV line with the D5W solution.

Label the bag with appropriate identification.

Study Drug can be administered via a central venous line for continuous intravenous infusion or a secure peripheral line may be used. This decision is at the discretion of the Investigator. The infusion should be administered over 2 hours preferably using an infusion pump. Dosing solutions and volumes for OGX-427 dose modifications are in the table below:

Dose Solutions and Volumes for Study Drug for Dose Modifications

Initial Dose	Dosage Modification	# of vials	Volume of OGX-427	Volume of D5W
600mg	500mg	2.5	20 mL	20 mL
	400 mg	2	16 mL	24 mL

8.1.3 Precautions and Risks Associated with OGX-427

The risks and side effects that have been seen in patients who have been treated with OGX-427 alone that have been felt to be possibly, probably, or definitely related to Study Drug are defined below.

Very likely (greater than 20% of patients):

- Infusion reactions, which occur during or soon after the infusion of OGX-427, have occurred in ~ 67% of patients, including cytokine release syndrome, when the loading dose was 600 mg and the patient was premedicated with an H2 antagonist and antihistamine. The most common symptoms have been chills, flushing, diarrhea, nausea, and vomiting. The majority of reactions occurred with the first three loading doses and during the first weekly infusions of therapy. Reactions have continued to occur with further infusions in some patients. Reactions may require treatment or prophylaxis with corticosteroids. On rare occasions, infusion reactions can be life-threatening.
- Anemia
- Lymphopenia
- Decrease leukocytes

- Transient prolongation of PPT or elevated INR
- Decrease in kidney function
- Blood creatinine increased
- Decrease in liver function (reversible)
- Hyponatremia
- Elevated ALT
- Thrombocytopenia
- Hypokalemia
- Hyperglycemia
- Nausea
- Diarrhea
- Fatigue

Less likely (5-20% of patients):

- Pyrexia
- Decreased appetite
- Vomiting
- Pruritus
- Peripheral neuropathy
- Arthralgia
- Dizziness
- Hypertension
- Neutropenia
- Headache
- Myalgia
- Elevated bilirubin
- Muscle weakness
- Hematuria
- Influenza like illness
- Urticaria
- Dyspnea
- Abdominal pain
- Erythema
- Chest pain
- Rash
- Redness of the skin
- Cytokine release syndrome, which occurs during or soon after the infusion of OGX-427.
- Increased sweating or perspiration
- Feeling of intense heat

Rarely (but may be serious) (less than 5% of patients):

- Cerebral hemorrhage
- Thrombosis
- Pulmonary embolus
- Vascular purpura
- Hemolytic uremic syndrome (HUS)
- Pancreatitis
- Anaphylaxis or severe infusion reaction
- Hemoptysis
- Serious infection such as sepsis, pneumonia, abscess
- Arrhythmia
- Cardiac arrest
- Gastrointestinal hemorrhage
- Intestinal obstruction
- Status epilepticus
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Membranous nephropathy
- Hypovolemic shock
- Anasarca
- Pyelonephritis
- Sudden death

8.2 Pemetrexed

Pemetrexed is FDA approved for NSCLC. Commercials supplies will be used for this trial and the drug will not be provided. Refer to the prescribing information for additional information.

8.2.1 Labeling, Packaging and Supply

See full prescribing information for pemetrexed for complete details.

8.2.2 Preparation and Administration of Pemetrexed

See full prescribing information for pemetrexed for complete details.

8.2.3 Precautions and Risks Associated with Pemetrexed

See full prescribing information for pemetrexed for complete details.

8.3 Carboplatin

Commercial supplies of carboplatin will be used for this trial and the drug will not be provided. Refer to the prescribing information for additional information.

8.3.1 Labeling, Packaging and Supply

See full prescribing information for carboplatin for complete details.

8.3.2 Preparation and Administration of Carboplatin

See full prescribing information for carboplatin for complete details.

8.3.3 Precautions and Risks Associated with Carboplatin

See full prescribing information for carboplatin for complete details.

9 RESPONSE EVALUATIONS AND MEASUREMENTS

9.1 Patients with Measurable Disease

All subjects with measurable disease will be evaluated for response using the RECIST version 1.1 (Appendix E) (Eisenhauer et al. 2009).

10 STATISTICAL CONSIDERATIONS

10.1 Analysis Population

Sample size considerations are based on PFS and follow-up considerations are based on OS. The median PFS in the control group (carboplatin with pemetrexed plus placebo) is estimated to be approximately 5 months. A PFS target hazard ratio (HR) of 0.60, corresponding to a median PFS in the experimental group (carboplatin with pemetrexed plus OGX-427) of 8.3 months is hypothesized. The study will have 85% power to test this hypothesis using a one-sided log-rank at the 5% level of significance. Based on a uniform 15-month accrual period, a minimum of approximately 12 months follow-up period for PFS and a loss to follow-up/nonevaluability for PFS assessment rate of approximately 10% per year, a total of 155 subjects will be randomized in a 1:1 manner to achieve the targeted number of events in the scheduled PFS follow-up time. Sample size and power calculations were performed using PASS 2008 software.

10.2 Sample Size Considerations

All statistical analyses will be performed using SAS 9.1 or higher.

10.2.1 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics for continuous variables, and frequencies and percentages for categorical variables.

10.2.2 Stratification Factors

Randomization will be stratified by histology and smoking status for the purpose of balance in enrollment and exploratory analysis only. The stratification factors for this study are:

Histology: Large cell carcinoma or adenocarcinoma. Patients with mixed squamous/non-squamous histology are permitted provided the predominant histology is non-squamous and are to be stratified as adenocarcinoma. Patients with NOS designation or small-cell elements are not permitted.

Smoking Status: Patients will be stratified as smokers or non-smokers. Patients with a lifetime history of <100 cigarettes are stratified as non-smokers. Patients with history of smoking but have not smoked for >15 years are also considered non-smokers. All others will be classified as smokers.

10.2.3 Efficacy Analyses

All efficacy parameters will be analyzed using the intent-to-treat (ITT) population. Efficacy parameters may be additionally analyzed using the Safety population if more than 10% of randomized subjects do not receive study treatment.

The efficacy endpoints are PFS (primary) and the objective response rate (ORR) and OS (secondary).

10.2.4 Primary Efficacy Endpoint

Progression-free survival (PFS) is defined as the time (in months) from the date of randomization to the date of the first observation of progression based on radiologic assessment (RECIST criteria version 1.1) or date of death, whatever the cause, in the absence of progressive disease (PD), or censored at the date of last adequate tumor assessment.

The primary analysis is to conduct a comparison of PFS between the OGX-427 and placebo groups in the ITT population using the unstratified log-rank test. The primary analysis will be conducted at the time when at least 117 PFS events have been accumulated for the study. In addition, the hazard ratio (OGX-427: placebo) and corresponding two-sided 95% confidence interval (CI) will be estimated based on a Cox proportional hazards model using treatment group as the predictive factor. Each treatment group will be summarized using Kaplan-Meier curves, along with the respective median time point and two-sided 95% confidence interval obtained from the product-limit estimates.

10.2.5 Secondary Efficacy Endpoints

Objective response rate (ORR) is defined as the proportion of subjects with objective evidence of a CR or a PR using RECIST criteria version 1.1. ORR for each treatment group will be presented as the point estimate along with two-sided 95% confidence intervals calculated using both asymptotic normal approximation and exact binomial methods. Comparison of ORR between the OGX-427 and placebo treatment groups will be performed using Fisher's exact test.

Overall survival (OS) is defined as the time (in months) from the date of randomization to the date of death, due to all cause, or censored at the date last known alive. OS between the OGX-427 and placebo groups in the ITT population will be compared using the unstratified log-rank test. Each treatment group will be summarized using Kaplan-Meier curves, along with the respective median time point and two-sided 95% confidence interval obtained from the product-limit estimates.

10.2.6 Safety Analyses

All safety parameters will be summarized using the Safety population.

Safety assessments will consist of monitoring and recording protocol-defined AEs and serious adverse events (SAEs); measurement of protocol specified hematology, and clinical chemistry variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation.

The analyses of safety will be based on the frequency of adverse events and their severity. Worst toxicity grades per patient will be tabulated for select adverse events and laboratory measurements by using NCI CTCAE criteria v4.0.

10.3 Analysis Populations

The analysis populations for this study are the ITT and Safety populations.

Intent-to-Treat (ITT) population will consist of all randomized subjects.

Safety population will consist of all randomized subjects who received at least one dose of study treatment.

10.4 Planned Interim Analysis

No interim analyses are planned.

10.5 Data Safety Monitor

Safety monitoring will be performed by an independent Data Safety Monitor (DSM) who will be designated for this study since this will be the first evaluation of OGX-427 in combination with carboplatin and pemetrexed. A complete DSM review will occur after the first 12 patients have been enrolled (6 patients per treatment arm) and treated for at least one cycle to assess the frequency of ≥ Grade 3 adverse events and all serious adverse events. In addition, a second review will occur after the next 12 patients have been enrolled, for a total of 24 patients. The frequency of further safety reviews will be determined by the DSM based on these early safety reviews.

The primary responsibility of the DSM will be overall safety for patients on the protocol. The DSM will monitor the safety of individual patients during the entire adverse event reporting period (i.e., from the first administration of Study Drug through 30 days after completion of study treatment). The sponsor will provide the DSM with a copy of any unexpected Study Drug-related SAE Report Form within 15 business days of receipt by the sponsor. The sponsor will also provide the DSM with copies of all expedited SAE reports submitted to regulatory agencies.

In addition, the DSM will:

- Perform periodic reviews of all safety data for individual patients. These listings would be based on the available safety data in the clinical study database and will include: demographic characteristics, general medical history (including concurrent illnesses), disease history, Study Drug administration, vital signs during infusion, clinical laboratory data (serum chemistry, hematology), and reported adverse events.

- Perform continued monitoring of Grade 3 and higher adverse events and SAEs on an ongoing basis for all patients.
- Perform toxicity reviews of the first 6 patients enrolled in Group 1 (OGX-427) for dose-limiting toxicities (DLTs) and the need for one dose-level reduction for weekly OGX-427 for the remainder of the study as defined in Section 10.5.1.

10.5.1 Dose-Limiting Toxicity

If in the opinion of the Data Safety Monitor, DLTs that are likely to have resulted from exposure to OGX-427, the DSM may modify the OGX-427 dose in Group 1. If the first six (6) patients enrolled in the OGX-427 group have 2 or more DLTs during Cycle 1, the weekly dose of 600 mg of OGX-427 should be reduced for the remainder of the study to 500 mg for all patients. There will be one dose reduction allowed for patients starting OGX-427 treatment at the weekly dose of 500 mg (Table 4). The loading dose will remain at 600 mg.

Dose-limiting toxicities will be defined as follows:

- Grade 4 neutropenia or thrombocytopenia lasting >7 days; Grade ≥3 febrile neutropenia; and Grade ≥3 thrombocytopenia with Grade >2 hemorrhage;
- Grade ≥ 3 non-hematologic toxicity with the exception of:
  - Fatigue, malaise, lethargy, anorexia
  - Grade ≥3 diarrhea or nausea that resolves to ≤ Grade 2 within 48 hours
  - Grade ≥3 ALT/AST elevation that resolves to ≤ Grade 2 within 7 days
  - Grade 3 pulmonary embolus
  - Grade 3 hyperglycemia in patients with known diabetes mellitus
- Treatment delay of ≥21 days due to unresolved toxicity

11 SAFETY REPORTING AND ANALYSES

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB.

11.1 Adverse Events

The PI is responsible for recognizing and reporting AEs (see Section 11). It is SCRI Innovation's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. Oncogenex will be responsible for reporting to international regulatory bodies.

11.1.1 Definitions of Adverse Events

An AE is the development of an undesirable medical condition, or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings).

11.1.2 Recording and Reporting of Adverse Events

All AEs of any subject during the course of the study will be recorded in the CRF, and the investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE 4.0.

If the AE is serious, it should be reported immediately to SCRI Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a study-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant CRF.

Test findings will be reported as an AE if the test result requires an adjustment in the study drug(s) or discontinuation of treatment; and/ or test findings require additional testing or surgical intervention; a test result or finding is associated with accompanying symptoms; or a test result is considered to be an AE by the investigator.

All AEs regardless of seriousness or relationship to study treatment, spanning from the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that subject, are to be recorded in the CRF.

11.1.3 Handling of Adverse Events

All AEs resulting in discontinuation from the trial should be followed until resolution or stabilization. Subjects must be followed for AEs for 30 calendar days after discontinuation or completion of clinical trial-specific treatment (e.g., chemotherapy, radiation, oral medications, targeted therapy, and surgery). All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the subject's medical record and as a comment on the CRF. After 30 days of completion of study-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.2 Serious Adverse Events

11.2.1 Definitions of Serious Adverse Events

The definitions of SAEs are given below. The Principal Investigator is responsible for ensuring that all staff involved in the trial are familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that: results in death, is immediately life-threatening, requires at least a 24-hour inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial), does not require reporting as an SAE to the SCRI Innovation Safety Department. Deaths that are attributed by the Investigator solely to the progression of disease do not require reporting as an SAE to the SCRI Innovations Safety Department.

11.2.2 Serious Adverse Event Reporting by Investigators

It is important to distinguish between "serious" and "severe" adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be

considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the CRF and SAEs on the SAE Report Form.

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to SCRI Innovations Safety Department in order to comply with regulatory requirements. Serious adverse events may occur at any time from the start of study treatment through the 30-day follow-up period after the last study treatment. SCRI Innovations Safety Department must be notified of all SAEs, regardless of causality, within one business day of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, the SAE Report Form should be completed with the necessary information. All SAEs occurring from the start of study treatment, until 30 calendar days of last study treatment must be reported to the SCRI Innovations Safety Department as SAEs on the SAE Report Form and followed until resolution (with autopsy report if applicable).

Deaths and other SAEs occurring >30 calendar days after last study treatment that are deemed 'possibly' or 'probably' related to study drug must be reported as SAEs on the SAE Report Form within 1 day of first knowledge of the event by the treating physician or research personnel (with an autopsy report if available).

Deaths occurring >30 calendar days after last study treatment and not attributed to study treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate CRF.

To report an SAE, the SAE Report Form should be completed with the necessary information.

The SAE report Form should be sent to SCRI Innovations Safety Department via fax or e-mail using the following contact information (during both business and non-business hours):

SCRI Innovations Safety Department

Safety Dept. Phone #: 615-329-7358

Safety Dept. Fax #: 866-807-4325

Safety Dept. Email: CANN.SAE@scresearch.net

Transmission of the SAE report Form should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Innovations Safety Department as soon as it is available; these reports should be submitted using the SCRI Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the trial reference manual.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB.

11.2.3 Sponsor Serious Adverse Event Reporting Requirements

This section applies solely to SCRI Development Innovations

The Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonization (ICH) guidelines, FDA regulations, and/or local regulatory requirements.

The Sponsor will fax within one business day copies of the SCRI Innovations SAE Reporting Form for all SAEs that occur during the trial to the pharmaceutical company(ies) (i.e., OncoGenex Technologies, Inc) that are supporting the trial. Follow-up reports and information for non-serious AEs that become serious will also be faxed to the pharmaceutical company(ies). If applicable, copies of investigational new drug (IND) Safety Reports and Medwatch 3500A form(s) submitted to the FDA will be faxed to the pharmaceutical companies as applicable. Reporting information and requirements specific to the pharmaceutical company(ies) who are supporting this trial are listed below.

Safety reporting will be communicated to OncoGenex Technologies, Inc. using the contact information below:

OncoGenex Technologies, Inc
Phone: 425-686-1500
Fax: 425-686-1600

The Sponsor is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the regulatory agencies and competent authorities via telephone or fax within 7 calendar days after being notified of the event. The Sponsor will report all related but unexpected SAEs including non-death/non-life-threatening SAEs associated with the use of the trial medications to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/Ethics Committees (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

11.2.4 Sponsor Reporting for Trials under an Investigational New Drug Assignment

All written IND Safety Reports submitted to the FDA by the Sponsor must also be faxed to pharmaceutical company(ies) that are supporting the trial:

OncoGenex Technologies, Inc.
Phone: 425-686-1500
Fax: 425-686-1600

11.3 Recording of Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Form and AE CRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE CRF; AEs that meet the definition of an SAE should additionally be reported following the procedures noted in Section 11.2.

11.3.1 Diagnosis vs. Signs and Symptoms

All AEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE CRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the SAE Report Form and/or the AE CRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE CRF.

A recurrent AE is one that occurs and resolves between subject evaluation timepoints, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE CRF.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant CRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE CRF.

Abnormal laboratory values will be reported as an AE if the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment; and/ or laboratory findings require additional testing or surgical intervention; a laboratory result or finding is associated with accompanying symptoms; or a laboratory result is considered to be an AE by the investigator.

11.3.4 Deaths

Deaths that occur during the study-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Trial Discontinuation"

CRF. All other on-trial deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the SCRI Innovations Safety Department.

When recording an SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event page of the CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the CRF Adverse Event page. During post-trial survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" CRF.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of preexisting hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE (refer to Section 11.2).

11.3.6 Pre-Existing Medical Condition

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the General Medical History CRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an SAE Report Form and/or AE CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to Section 11.4 for specific instructions.

11.3.8 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (See Section 11.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the subject into the trial. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.4 Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously (see Section 11.2):

<u>Pregnancy, Abortion, Birth Defects/Congenital Anomalies:</u>

If a subject becomes pregnant while enrolled in the trial, a Pregnancy Form (a paper report form) should be completed and faxed to SCRI Innovations Safety Department. If a pregnancy is confirmed, the subject must not receive any study drug(s), and must be discontinued from the

trial. SCRI Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to SCRI Innovations Safety Department.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

Pemetrexed, Carboplatin or OGX-427 Overdose

Symptomatic and non-symptomatic overdose must be reported in the CRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to SCRI Innovations Safety Department within one working day using the corresponding screens in the CRF, and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of OGX-427, see the Investigator Brochure.

For information on how to manage an overdose of pemetrexed, see the Package Insert.

For information on how to manage an overdose of carboplatin, see the Package Insert.

12 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

12.1 Institutional Review Board Approval

The trial protocol, ICF, IB, available safety information, subject documents (e.g., trial diary), subject recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the subjects and documentation evidencing the PI's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the trial start.

The PI/Study Chair/Sponsor/CRO and/or designee will follow all necessary regulations to ensure appropriate, initial, and ongoing, IRB trial review. The PI/Study Chair/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates provided by OncoGenex for OGX-427, will be prepared by the Sponsor or its representative as required, for submission to the relevant IRB.

12.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, the

Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

Safety updates provided by OncoGenex for OGX-427 will be prepared by the Sponsor or its representative as required, for submission to the relevant regulatory authority.

12.3 Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

12.4 Informed Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

The informed consent form will be submitted for approval to the IRB that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the subject's medical record. A copy of the informed consent form, to include the subject's signature, will be provided by the investigator to the subject.

If an amendment to the protocol substantially alters the trial design or the potential risks to the subjects, the subject's consent to continue participation in the trial should be obtained.

12.4.1 Confidentiality

12.4.2 Subject Confidentiality

Confidentiality of subject's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the trial, a subject must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from subjects in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;

- The information collected about the research trial will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization.

In the event that a subject revokes authorization to collect or use his or her 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 trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the subject's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and initials will identify subjects on the CRF or other documents submitted to the Sponsor. This information, together with the subject's date of birth, will be used in the database for subject identification. Subject names or addresses will not be entered in the CRF or database. No material bearing a subject's name will be kept on file by Sponsor. Subjects will be informed of their rights within the ICF.

12.4.3 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

12.5 Financial Information

SCRI Innovations is sponsoring this trial. OncoGenex Technologies, Inc. will provide funding to SCRI Innovations for this trial. OncoGenex Technologies, Inc. will provide the study drug OGX-427 for study participants. The physicians participating in this study will receive compensation from SCRI Innovations**.**

13 RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

13.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of OncoGenex Technologies and

the Study Chair supporting the trial. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to trial design, risk to subject, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by SCRI Innovations as applicable, after IRB approval and specifically when an increase to dosing or subject exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and/or FDA approval include, but are not limited to, the following:

- Change to trial design
- Risk to subjects
- Increase in dose or subject exposure to drug
- Subject number increase
- Addition or removal of tests and/or procedures
- Addition/removal of an Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the subjects, their consent to continue participation in the study should be obtained.

13.2 Documentation Required to Initiate Study

Before the study may begin, certain documentation required by FDA regulations must be provided by the Investigator.

Documents at a minimum required to begin a trial in the US include, but are not limited to, the following:

- A signature-authorized contract;
- A copy of the official IRB approval of the trial and the IRB members list;
- Current Curricula Vita for the Principal Investigator and any associate investigator(s) who will be involved in the trial;
- Indication of appropriate accreditation for any laboratories to be used in the trial and a copy of the normal ranges for tests to be performed by that laboratory;
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed;
- A copy of the IRB-approved consent form containing permission for audit by representatives of SCRI Innovations, the IRB, and the FDA;
- Financial disclosure forms for all investigators listed on Form FDA 1572;

- Site qualification reports, where applicable;
- Verification of Principal Investigator acceptability from local and/or national debarment list(s) (to be performed and documented by SCRI Innovations).

13.3 Trial Documentation and Storage

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the subject's CRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the subject's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and trial staffs are responsible for maintaining a comprehensive and centralized filing system (Site Trial File/SSF or ISF) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed CRFs, IRB approval documents, Financial Disclosure forms, subject identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories and any other trial-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing

application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating subjects (sufficient information to link records e.g., CRFs and medical records), all original, signed informed consent forms, and copies of all CRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). SCRI Innovations will notify the investigator(s)/institutions(s) when the trial-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the trial, both SCRI Innovations should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

13.4 Data Collection

The trial CRF is the primary data collection instrument for the trial. CRFs will be completed using the English language and should be kept current to enable the sponsor to review the subjects' status throughout the course of the trial.

In order to maintain confidentiality, only trial number, subject number, initials and date of birth will identify the subject in the CRF. If the subject's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI Innovations and replaced instead with the subject number and subject's initials. The investigator will maintain a personal subject identification list (subject numbers with corresponding subject identifiers) to enable records to be identified and verified as authentic. Subject data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested on the CRF must be supported by and be consistent with the subject's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the CRF, a note should be created verifying that the field was "Not done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will electronically sign and date the subject CRF casebook indicating that the data in the CRF has been assessed. Each completed CRF will be signed and dated by the PI, once all data for that subject is final.

13.5 Trial Monitoring, Auditing, and Inspecting

Participation as an Investigator in this trial implies the acceptance of potential inspection by government regulatory authorities, the Sponsor, or its representative(s).

At the Sponsor's discretion Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

13.6 Quality Assurance and Quality Control

Each trial site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for trial conduct, data generation and collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

13.7 Disclosure and Publication Policy

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. SCRI Innovations reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the SCRI Innovations publication strategy. Oncogenex will review any materials for publication prior to submission.

SCRI Innovations will register the trial on *www.clinicaltrials.gov*. In addition, SCRI Innovations will publish the results of the trial.

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15 APPENDICES

Appendix A: ECOG Performance Status Criteria

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

Appendix B: Guidelines for Women of Child-Bearing Potential

Women of Child-Bearing Potential are Defined as Follows:

- Any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential".

Women Not of Childbearing Potential are Defined as Follows:

- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
- Women who are >45 years of age, not using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L)
- Women who are >45 years of age, using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone replacement therapy

Acceptable Contraception Methods:

Male subjects with female partners of child-bearing potential and women subjects of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the trial and for 6 months (women) or 6 months (men) following discontinuation of study treatment. Male subjects must also refrain from donating sperm for 6 months following discontinuation of study treatment.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

The following are acceptable forms of secondary contraception, when used with a barrier method and spermicide:

- True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception

- Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- Placement of an intrauterine device (IUD) or intrauterine system (IUS), with the exception of IUD progesterone T

The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Appendix C: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix D: LUN 229 Schedule of Assessments

Assessments	Pre-Treatment	Loading Dose	Study Treatment Phase (Cycle = 21 days)					Maintenance Phase[j]			Off-Treatment	Follow-Up	
			Cycle 1		Cycle 2-4		Restage End of Cycles 2 and 4 (±7d)	Days		Restage Every 2 Cycles (±7d)	End of Study Treatment[k]	Off Treatment Prior to Progression[l]	After Disease Progression[m]
	Baseline[a]	Days -9 to 0	Days 1	Days 8/15	Days 1	Days 8/15		1	8/15				
TESTS AND OBSERVATIONS													
Informed consent	X												
Medical history and demographics	X												
Smoking history	X												
Physical exam and weight[b]	X		X		X			X			X	X	
Vital signs[c]	X	X	X	X	X	X		X	X		X	X	
ECOG PS	X		X		X			X			X	X	
ECG[e]	X												
Adverse event evaluation		X	X	X	X	X		X	X		X		
Concomitant medication review	X	X	X		X			X	X		X	X	
Survival status													X
LABORATORY EVALUATIONS													
CBC, 3-part differential, platelets	X		X	X	X	X		X	X		X		
CMP[d]	X		X	X	X			X			X		
Serum or urine pregnancy test[f]	X												
Correlative serum testing[g]	X	X	X		X			X			X		
Archive tissue collection[g]	X												
STAGING													
CT Scan of Chest w/adrenals[l]	X						X[h]			X[h]	X	X	
CT Scan of Abdomen/Pelvis[l]	X						X[h]			X[h]	X	X	
PET Scan or Bone Scan	X												
MRI Brain or Head CT Scan	X												

a The physical examination, medical history, concomitant medications recorded ≤30 days prior to trial entry, ECOG PS, CBC, CMP, and 12-lead ECG should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours prior to the initiation of treatment they do not have to be repeated. Scans to document evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment. The smoking history should be recorded at the baseline visit.

b Physical examination will include measurements of height and weight at the baseline visit. Physical examinations (PE) done at all other times during the trial will include only measurements of weight.

c Vital signs (resting heart rate, blood pressure, oral temperature) will be collected at baseline and prior to each dose of OGX-427, and at anytime there are signs or symptoms of an infusion reaction.

d CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

e ECG at baseline. Repeat if clinically indicated.

f Pregnancy tests will only be performed in women of childbearing potential ≤72 hours prior to first dose of study treatment.

g Correlative testing will include the collection of archival tumor tissues and blood samples. Blood samples will be collected from all patients and assessed for serum levels of Hsp27. At these time points, approximately 7 mL of blood will be collected (red topped tube). In addition, a paraffin-embedded tumor tissue block (from the primary tumor or metastasis) obtained at diagnosis may be used for correlative testing. In the absence of paraffin-embedded tissue, 15 unstained paraffin-embedded tumor slides are acceptable.

h Patients will be restaged after every 2 cycles (every 6 weeks, ±7days) during Study Treatment Phase and Maintenance Phase. Patients with progressive disease or unacceptable toxicity should be discontinued from the study; patients with stable disease or response to therapy will continue treatment.

i If adrenal glands are not captured in the CT scan of the chest, then a CT scan of the abdomen and pelvis will be required.

j Patients without evidence of undue toxicity may continue treatment with study drug (OGX-427 or placebo) and pemetrexed until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy.

k After patients complete therapy or are discontinued from the study they will visit the study center ≤30 days after finishing treatment for end-of-treatment assessments. All patients will be followed during the off -treatment period until all treatment related toxicity resolves, and for at least 30 days post-study drug discontinuation.

l Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 6 weeks from the date of last dose of trial drug until disease progression or for up to 2 years whichever comes first.

m Patients with documented disease progression will be followed every 2 months for survival status (e.g., date and cause of death) for up to 2 years or death whichever comes first. Patients may be contacted during outpatient visits or by telephone.

Appendix E: Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Subjects with Measureable Disease

Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT scan (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest X-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with >10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, and abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging requirements.

Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of >15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

15.1.1 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per study screening requirements.

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

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI:	CT is the best currently available and reproducible method to measure target lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. MRI of the chest should only be performed in extenuating circumstances. Even if IV contract cannot be administered (for example, in the situation of allergy to contract), a non-contrast CT of the chest is still preferred over MRI.
Ultrasound:	Ultrasound should not be used to measure tumor lesions. Ultrasound may be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy should not be used to measure tumor lesions. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers are not used to assess response in this protocol.
Cytology and Histology:	Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

15.1.2 Response Criteria

Evaluation of Target Lesions

Complete Response:	Complete disappearance of all target lesions. Any pathological lymph node (target or non-target) must have a reduction in short axis to < 10 mm).
Partial Response:	A decrease from baseline of ≥30% of the diameter(s) of all target lesions.
Stable Disease:	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of the diameters of target lesions while on study.
Progressive Disease:	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum while on study (this includes the baseline sum if that is the smallest on study), or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response:	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
Stable Disease:	Persistence of one or more non-target lesions.
Progressive Disease:	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the subject also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD
NE	SD	NO	NE

CR=complete response; NE=not evaluable; PD = progressive disease; PR=partial response; SD=stable disease.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the Case Report Form (CRF).