A NON-RANDOMIZED PHASE IB-II PROTOCOL OF PACLITAXEL, CARBOPLATIN AND THE DUAL PI3K/MTOR KINASE INHIBITOR, PF-05212384 (GEDATOLISIB), FOR PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL CARCINOMA OF THE LUNG

Protocol Number:	**UF-STO-LUNG-002**
Coordinating Center:	University of Florida
Principal Investigator:	Dennie Jones, MD 1601 SW Archer Road Gainesville, FL 32608-1135 Telephone: 352-548-6000, ext. 4320 Fax: 352-548-6463 E-mail address: Dennie.Jones@medicine.ufl.edu Dennie.Jones@VA.gov
Co-Investigators:	Fred Kaye, MD Jennifer Duff, MD David DeRemer, PharmD
Statistician:	Susan McGorray, PhD
Protocol Managers:	Allison Allegra, MPH Alisha Daniels, MD
Clinical Phase:	Phase I-II
IND Status:	IND 132757
Investigational Agent:	**Gedatolisib**
Date of Original Protocol:	June 22, 2016
Date of Current Protocol:	January 10, 2019
Version of Current Protocol:	Version 1.9

CONFIDENTIAL
The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless law or regulations require such disclosure. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them

ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase (also SGPT)
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate transaminase (also SGOT)
AUC	area under curve
BID	two times daily
BSA	body surface area
BUN	blood urea nitrogen
C_{max}	maximum serum concentration
C_{peak}	peak concentration
CBC	complete blood count
CBR	clinical benefit response
CL	clearance
CMP	comprehensive metabolic panel
CNS	central nervous system
CR	complete remission
CRC	colorectal cancer
CRF	case report form
CRM	continual reassessment method
CT	computed tomography
CTC	common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
dL	deciliter(s)
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EU	European Union
FDA	Food & Drug Administration
FDG	fluorodeoxyglucose
FIP	first-in patient or Phase 1
FOB	functional observational battery
FSH	follicle stimulating hormone
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
gp	glycoprotein
HEK	human embryonic kidney
hERG	human ether-à-go-go related gene
Hgb	hemoglobin
HIV	human immunodeficiency virus

HRT	hormone replacement therapy
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IIR	investigator initiated research
IBR	Institutional Review Board
IV	intravenous
IWG	International Working Group
kg	kilogram(s)
LDH	lactic dehydrogenase
LIC	lead-in cohort
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mCRC	metastatic colorectal cancer
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
mg	milligram(s)
ml	milliliter(s)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
PCR	polymerase chain reaction
PD	pharmacodynamics
PET	positron emission tomography
PFS	progression-free survival
PH	pleckstrin homology
PI	principal investigator
PI3K	phosphatidylinositol 3-kinase
PIP2	phosphatidylinositol (4,5)-bisphosphate
PIP3	phosphatidylinositol (3,4,5)-trisphosphate
PK	pharmacokinetics
PO	orally
PR	partial remission
PT	prothrombin time
PTT	partial thromboplastin time
Q	every
QD	once daily
Q2W	every two weeks
Q3W	every three weeks
QW	once weekly
RBC	red blood cells
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose

SAE	serious adverse event
SC	subcutaneous
SD	stable disease
S-D	Sprague-Dawley
SGOT	serum glutamic oxaloacetic transaminase (also AST)
SGPT	serum glutamic pyruvate transaminase (also ALT)
t½	half-life
T_{max}	time to maximum plasma concentration
TMZ	temozolomide
UF	University of Florida
UFHCC	University of Florida Health Cancer Center
US	United States
VAMC	Veterans Affairs Medical Center
WHO	World Health Organization
WOCBP	women of childbearing potential

PROTOCOL SIGNATURE PAGE

A NON-RANDOMIZED PHASE IB-II PROTOCOL OF PACLITAXEL, CARBOPLATIN AND THE DUAL PI3K/MTOR KINASE INHIBITOR, PF-05212384 (GEDATOLISIB), FOR PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL CARCINOMA OF THE LUNG

Principal Investigator:

Signature of Investigator	Date

Dennie Jones, MD
Printed Name of Investigator

University of Florida
Name of Facility

Gainesville, Florida
Location of Facility (City/State)

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

PROTOCOL SYNOPSIS

<table>
<tr><td>Title:</td><td>A NON-RANDOMIZED PHASE IB-II PROTOCOL OF PACLITAXEL, CARBOPLATIN AND THE DUAL PI3K/MTOR KINASE INHIBITOR, PF-05212384 (GEDATOLISIB), FOR PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL CARCINOMA OF THE LUNG</td></tr>
<tr><td>Rationale:</td><td><u>Background</u>: Approximately 70% of patients with unresectable non-small cell lung cancer (NSCLC) who receive and progress through frontline chemotherapy will be eligible for second line treatments. Any of the agents which are available for frontline therapy can be used in the salvage setting, though only erlotinib, docetaxel (with or without ramicirumab), and pemetrexed (in non-squamous cell carcinoma) are FDA-approved in the salvage setting based upon their demonstrated survival benefit in randomized phase III trials. All of these appear to be roughly equivalent in terms of clinical benefit, which is admittedly modest, with response rates <10%, clinical benefit rates of approximately 50%, and overall survivals of approximately 6 months. Still, a substantial number of patients may not benefit from the agents in the salvage treatment setting, thus it is critical to identify those patients who stand to benefit the most.

<u>Hypothesis</u>: The use of PF-05212384 in escalating dose cohorts, in combination with standard paclitaxel and carboplatin in subjects with NSCLC will be tolerated in a dose and schedule which will be supportive of a subsequent phase II trial, where the combinations will be associated with a clinical benefit (objective response, disease stability, and time to progression) in patients with evidence of aberrant PI3K or mTOR activation.</td></tr>
<tr><td>Study Schema: Drugs / Doses / Length of Treatment</td><td>
<table>
<tr><td>Dose Cohort</td><td>PF-05212384 Dose (mg, days 2, 9, 16)</td></tr>
<tr><td>1</td><td>110</td></tr>
<tr><td>2</td><td>150</td></tr>
<tr><td>3</td><td>180</td></tr>
</table>
<table>
<tr><td>Paclitaxel</td><td>200 mg/m^2</td><td>3 hour IV infusion*</td><td>Q 21 days x 6 cycles</td></tr>
<tr><td>Carboplatin</td><td>AUC = 6</td><td>30 minute IV infusion immediately following paclitaxel</td><td>Q 21 days x 6 cycles</td></tr>
</table>
</td></tr>
<tr><td>Objectives:</td><td><u>Primary (Phase IB)</u>
• To identify the maximum tolerated dose of PF-05212384 in combination with paclitaxel and carboplatin in subjects with NSCLC.</td></tr>
</table>

<table>
<tr><td></td><td>Primary (Phase II)
• To estimate the objective rate of response of PF-05212384 in combination with paclitaxel and carboplatin administered to subjects with unresectable or metastatic NSCLC, according to current RECIST criteria.
Secondary
• To document the severity and reversibility of toxicities
• To estimate median duration of response
• To estimate progression-free survival for subjects on this trial with NSCLC treated with PF-05212384 in combination with paclitaxel and carboplatin
• To estimate the overall survival</td></tr>
<tr><td>Study Design:</td><td>The study will consist of two phases, Ib and II. The phase Ib portion will study dose escalations in separate 3+3 cohorts using the dose levels of PF-05212384 listed in the table below. The phase II portion will consist of a two stage Simon design. The doses for paclitaxel (200 mg/m^2, Q21 days) and carboplatin (AUC=6, Q21 days) do not adjust as part of the study design.

<table><tr><th>Dose Cohort</th><th>PF-05212384 Dose (mg, days 2, 9, 16)</th></tr><tr><td>1</td><td>110</td></tr><tr><td>2</td><td>150</td></tr><tr><td>3</td><td>180</td></tr></table>
During the first stage, cohorts of 3 participants each will be sequentially enrolled to each increasing dose level, beginning with dose level 1 (110 mg) until the first dose limiting toxicity occurs, or safely accrued to dose level 3. The level determined to be the maximal tolerable dose will have three additional subjects to better define tolerability prior to initiating the phase II portion. Once that happens, the first stage (phase Ib) will end and the trial will move to the second stage (phase II). During the second stage, initially 10 subjects will be enrolled; in the absence of grade 3-5 toxicity, if at least one response has been observed, then accrual will continue to a total of 41 subjects.</td></tr>
<tr><td>Accrual Goal:</td><td>A total of 41 subjects</td></tr>
<tr><td>Inclusion Criteria:</td><td>A. Signed IRB-approved informed consent prior to any study-related procedures
B. Age of 18 years or older
C. Advanced-stage unresectable NSCLC, as confirmed by pathological and/or radiological analysis (subjects will be classified as having advanced disease if they were not eligible</td></tr>
</table>

	for, or had disease progression after, surgical or locoregional therapies) D. Prior chemotherapy will be allowed for other invasive malignancies, provided therapy was completed at least five years before the start of protocol therapy, and participants have recovered from all toxicities of that prior therapy E. Participants may have received prior chemotherapy for NSCLC; in the phase I portion, subjects who have previously received paclitaxel and/or carboplatin will be allowed. In the phase II portion, subjects must not have received prior carboplatin or a taxane within the prior five years F. In the Phase II portion, subjects must have disease which lacks PTEN expression by immunohistochemistry, or has known prior activating PI3K or inactivating PTEN gene mutations (mutations will not be assayed for specifically) G. Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2 H. Life expectancy ≥ 12 week I. Participants must have measureable disease by RECIST criteria J. Absolute neutrophil count $\geq$ 1500 mm^3 (individuals with benign ethnic neutropenia may be enrolled if they have no evidence of infectious diathesis, or febrile neutropenia at the time of enrollment) K. Platelet count $\geq 100\times10^9$ L L. Hgb $\geq$ 8.5 g/dL (subjects may receive transfusions to achieve this, in the absence of overt bleeding) M. Total Bilirubin $\leq$ 2 mg/dL N. AST/ALT $\leq$ 3 times the upper limit of normal range O. Serum creatinine $\leq$1.5 times the upper limit of the normal range P. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for at least 6 months after the last dose of study drug to minimize the risk of pregnancy. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:

	• Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or • For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL. Q. Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (*e.g.*, abstinence, condoms, vasectomy) throughout the study and should avoid conceiving children for 6 months following the last dose of study drug.
Exclusion Criteria:	A. Uncontrolled cardiac disease, congestive heart failure, angina, arrhythmias or hypertension. B. Myocardial infarction or unstable angina within 2 months of treatment. C. Subjects who are carboplatin- or paclitaxel-resistant. D. Known human immunodeficiency virus (HIV) infection or chronic active Hepatitis B (subjects will not be screened for this). E. Active clinically serious infection > CTCAE Grade 2. F. Thrombotic or embolic events such as a cerebrovascular accident including transient ischemic attacks within the past 6 months. G. Pulmonary hemorrhage/bleeding event ≥ CTCAE Grade 2 within 4 weeks of first dose of study drug. H. Any other hemorrhage/bleeding event ≥ CTCAE Grade 3 within 4 weeks of first dose of study drug. I. Serious non-healing wound, ulcer, or bone fracture. J. Evidence or history of bleeding diathesis or coagulopathy K. Major surgery, open biopsy or significant traumatic injury within 4 weeks of first study drug L. Women or men of childbearing potential who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 6 months after the last dose of study drug M. Women who are pregnant or breastfeeding.

	N. History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician. O. Prisoners or subjects who are involuntarily incarcerated. P. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness. Q. Subjects demonstrating an inability to comply with the study and/or follow-up procedures.
Efficacy Assessments:	For the phase Ib portion of the study, efficacy is not a primary objective. For the phase II portion, clinical activity, in terms or rate of objective response, clinical benefit, progression-free survival, duration of response, and overall survival will be assessed. Activity of this regimen, as well as toxicity, will be assessed as follows: <u>On-Study Evaluations</u> a. Prior to initiating each treatment cycle b. Toxicity assessment, interim medical history and physical examination c. Laboratory studies: CBC with leukocyte differential count CMP d. Prior to initiating every other treatment cycle: CT, PET/CT or MRI scans to document tumor status.
Statistical Considerations:	<u>Determination of Sample Size</u> The trial will enroll up to 41 total subjects, 12 in the phase Ib portion and up to 29 in the phase II portion. In the phase II portion of the study, so we are interested in evaluating the feasibility and safety of a regimen of weekly PF-05212384 (gedatolisib) in combination with paclitaxel and carboplatin administered to subjects with non-small cell lung cancer. To minimize the number of subjects exposed, the sample size will be determined by the anticipated response rate. A response rate of 20% or above to PF-05212384 in combination with paclitaxel and carboplatin will be of interest in subjects with previously-treated squamous cell lung cancer. Initially, 10 subjects will be evaluated for response, and if none of the 10 evaluable subjects experiences a partial or complete response, then the study will be terminated. Otherwise, 19 additional subjects will be accrued for a total of 29. The null hypothesis will be rejected if 4 or more responses are observed in 29 subjects. This two stage Simon's design yields a type I error rate of

	0.047 and power of 0.8 when the true response rate is 0.2. A subject is considered eligible for toxicity evaluation if they have received at least one dose of PF-05212384, paclitaxel or carboplatin. A subject will be considered eligible for evaluation of activity if they have also received two cycles of therapy as planned. Statistical Analysis Plan. The maximum tolerated dose of PF-05212384, in combination with paclitaxel and carboplatin, will be determined by the dose escalation rules summarized in Sections 4.2 and 9.2. All subjects who received study drug will be included in the safety analysis of this combination regimen. Adverse event data and corresponding toxicity grades during treatment and during long-term follow-up will be summarized in the form of tables. Incidence tables will be generated to summarize incidence of subjects reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be displayed. Listings of adverse events by subjects will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. Safety data will be summarized for the overall subject group and by dose levels. Dose-toxicity curves will be fitted to the final data to estimate the toxicity rates of each dose levels. Analysis of Demographic and Baseline Characteristics The analysis of demographic characteristics (age, gender, tobacco abuse history and ethnicity) and baseline characteristics, including weight, performance status, and histologic subtype, will be primarily descriptive. They will be summarized in tabular format. Efficacy Analysis The primary endpoint of the phase Ib portion of this protocol is to determine a tolerable phase II dose of PF-05212384 in combination with paclitaxel and carboplatin. The primary endpoint of the phase II portion of this study is to determine the objective response rate of disease to the administration of PF-05212384 in combination with paclitaxel and carboplatin. A secondary endpoint of this study will be progression-free survival following PF-05212384 therapy. Kaplan-Meier mean estimates and survival curves of progression-free survival rates will be calculated. Secondary endpoints, including response

	rates, clinical benefit rate (CR + PR + SD), toxicities and reversibility of toxicities, will be estimated along with exact 95% binomial confidence intervals. <u>Safety Analysis</u> Subjects will be examined and graded each cycle for subjective/objective evidence of developing toxicity according to NCI-CTC toxicity criteria. Toxicities will be graded according to Common Toxicity Criteria (CTCAE) v4.0. Incidence tables will be generated to summarize incidence of subjects reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal, and incidence of serious adverse events. In the absence of significant treatment-related abnormalities, in subsequent courses subjects will not require weekly laboratory evaluation, but will require the documentation of return to baseline values prior to the initiation of subsequent courses of therapy. <u>Missing Data</u> Subjects lost to follow up along with other clinical variables without values are considered as missing data. We are not planning to do missing data imputation.
Estimated Enrollment Period:	24 months
Estimated Study Duration:	30 months

1.0 BACKGROUND

1.1 Lung Cancer Therapy

The current accepted frontline therapy for unresectable NSCLC is platinum-based therapy. In North America, most clinicians utilize carboplatin, whereas cisplatin is offered in other parts of the world. The standard of care for most "fit" patients with non-mutation positive NSCLC (Karnofsky performance status of 70%-100%) is doublet therapy with either cisplatin or carboplatin, along with either paclitaxel, docetaxel, vinorelbine, or gemcitabine. Certain subpopulations of patients with non-squamous cell carcinomas are often offered regimens containing pemetrexed and/or bevacizumab. However, in multiple randomized multi-institutional trials, each of the doublets has a comparable response rate of approximately 20%, median progression-free survival of 4-5 months, median overall survival of 8-10 months, and one year survivals of 35-40%. Approximately 70% of patients who receive and progress through frontline chemotherapy will be eligible for second line treatments. Any of the agents which are available for frontline therapy can be used in the salvage setting, though only erlotinib, docetaxel (with or without ramicirumab), and pemetrexed (in non-squamous cell carcinoma) are FDA-approved in the salvage setting based upon their demonstrated survival benefit in randomized phase III trials. All of these pharmaceutical agents appear to be roughly equivalent in terms of clinical benefit, which is admittedly modest, with response rates <10%, clinical benefit rates of approximately 50%, and overall survivals of approximately 6 months. However, selected epidermal growth factor receptor mutations are associated with much higher response rates of 50% to 70%, and prolonged median survivals of 17 to 38 months when treated with the EGFR tyrosine kinase inhibitor, erlotinib. [Jackman, et al., 2006; Rosell, et al., 2006] In a similar fashion, recent data has indicated superior benefit to the use of pemetrexed in nonsquamous NSCLCs. [Scagliotti et al., 2008; Scagliotti et al., 2009; Ciuleanu et al., 2009] There is an overwhelming need to develop regimens which are targeted to subgroups which may experience the most benefit from a specific agent.

1.2 PI3K/mTOR Signaling

Activation of phosphatidylinositol 3-kinase (PI3K) by activating mutations in the *PIK3CA* gene (encoding the p110α catalytic subunit of PI3K) or loss of the tumor suppressor PTEN (encoding a lipid and protein phosphatase) is associated with growth and progression of a number of cancers [Itoh, 2002; Kim, 2002; Sheng, 2003]. PI3K effects on tumor growth and progression are mediated by two key downstream effectors, Akt and mammalian target of rapamycin (mTOR) [Jiang and Liu, 2009]. Treatment with wortmannin or LY294002, general PI3K chemical inhibitors, increased apoptosis and inhibited growth of CRC cells [Powis, 1994;Ikezoe, 2007]; however, their use is limited due to toxicity *in vivo*. Selective inhibition of downstream proteins that are directly involved in survival and proliferation may allow more targeted treatment with fewer toxic effects. The deregulation of PI3K appears to be an early event in lung carcinogenesis, as it appears in cytologically normal bronchial epithelia [Gustafson, 2010]. However, while PI3K activation does not appear to be related to cigarette smoke exposure or chronic obstructive pulmonary disease, the level of activity is greater in smokers than in nonsmokers; this activation does not appear to be related to loss of PTEN expression of PI3K gene amplification [Gustafson, 2010]. PI3K mutations occur in lung cancer but appear to be uncommon; one study of 1125 cases demonstrated a PI3K mutation in only 2% of cases (n = 23), often in the setting of another oncogene mutation, such as

EGFR or K-RAS [Chaft, 2011]. To date, PI3K has not been a therapeutic target in the treatment of lung cancer, though preclinical data indicates that PI3K may be a valid therapeutic target, even with a concomitant K-RAS mutation [Engelman, 2008].

The mTOR protein is a key regulator of cell growth by controlling mRNA translation, ribosome biogenesis, autophagy and metabolism [Guertin and Sabatini, 2005; Mayer and Grummit, 2006; Iadevaia, 2012]. mTOR exists in two, distinct functional complexes: mTORC1 and mTORC2. mTORC1 consists of mTOR, mLST8 and RAPTOR (regulatory-associated protein of mTOR); mTORC2 consists of mTOR, mLST8, RICTOR (rapamycin-insensitive companion of mTOR), Sin1 and PROTOR/PRR5 (**Fig. 1**). When complexed with its cellular receptor, FKBP12 (FK506 binding protein-12), rapamycin, a macrocyclic lactone, binds directly to mTOR to inhibit mTORC1.

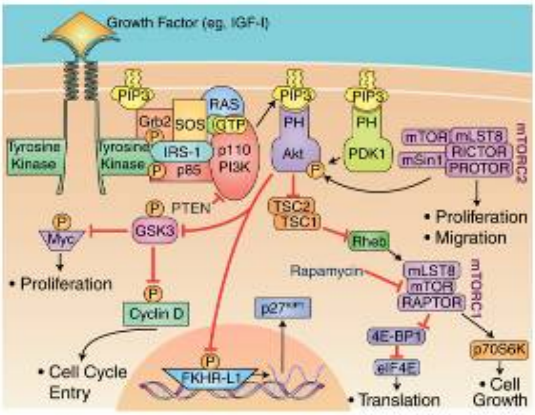


Fig. 1. Schematic diagram of PI3K/Akt/mTOR pathway.

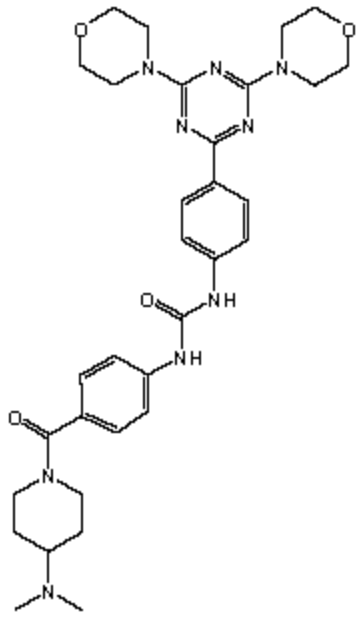
mTOR is a central modulator of proliferative signal transduction. Biomarkers indicate that the mTOR growth pathway is hyperactive in certain cancers suggesting mTOR as an attractive target for cancer therapy. Current dogma suggests that cancers, such as CRC, that are addicted to elevated Akt signaling are dependent upon downstream activation of mTOR signaling to drive tumorigenesis. Preclinical studies have shown that the mTOR pathway components mTOR, Raptor and Rictor are significantly over expressed in CRC tissues and cell lines.

1.3 **PF-05212384**

PI3K-α is a central component in the PI3K/Akt/mTOR signaling pathway. Activation of this pathway is associated with the initiation and maintenance of numerous tumor types, poor prognosis and poor survival in patients with various lymphatic tumors and cancers, and resistance to targeted anticancer therapies and conventional cytotoxic agents. PF-05212384 (PKI-587; WYE-129587; chemical name 1-[4-(4-Dimethylaminopiperidine-1-carbonyl)phenyl]-3-[4-(4,6-dimorpholin-4-yl-[1,3,5]triazin-2-yl)phenyl]urea) is a novel, pan class I dual inhibitor of PI3K and mTOR. PF-05212384 has been shown to decrease cell survival and proliferation and increase apoptosis in both in vitro and in vivo models, thus acting not only as a cytostatic agent but also as an agent that can cause tumor regression. The antitumor efficacy of PF-05212384 has been shown when used as a single agent and in combination with other anticancer therapies in continuous and intermittent dosing regimens. PF-05212384 is expected to prove effective in the treatment of human cancers in the clinical setting. PF-05212384 is being developed for the treatment of advanced solid tumors that have are known to have high occurrence mutations/alterations in the PI3K/mTOR pathway. PF-05212384 can be administered IV weekly or aligned with a patient's chemotherapy regimen and will be evaluated first as a monotherapy and then in combinations with other anticancer therapies. A single agent phase I dose of 154 mg/m2/week has been established [Shapiro, 2015].

Optimized regimens for PF-05212384 will be evaluated for safety, tolerability, and efficacy in patients with advanced solid tumors. PF-05212384 refers to the free base. The free base form will be used in the clinical studies.

Laboratory Code: PF-05212384
Molecular Weight: 615.73 Daltons (Da.)
Chemical Structure:



Chemical Name: 1-[4-(4-Dimethylaminopiperidine-1-carbonyl)phenyl]-3-[4-(4,6-dimorpholin-4-yl-[1,3,5]triazin-2-yl)phenyl] urea.
Molecular Formula: $C_{32}H_{41}N_9O_4$
Physical Description: White to beige powder

The drug product is a lyophilized powder or cake in a glass vial, which is to be reconstituted using an appropriate volume of sterile water for injection. After reconstitution, the solution is added to an appropriate volume of 5% dextrose injection for administration as an intravenous (IV) infusion. This formulation contains precedented excipients, with appropriate packaging and storage conditions.

1.3.1 Nonclinical Toxicity

Adverse effects in the 3-cycle dose-ranging and/or 8-cycle repeat-dose toxicity studies in rats and dogs included mortality (in rats); testicular tubular degeneration (in rats and dogs); weight loss (in rats and dogs); ulcerations of the skin (in rats); ulcerations in oral mucosa (in dogs); and decreases in thymic cellularity (in dogs). In the 8-cycle toxicity studies, animals were selected before initiation of dosing and assigned to a 12-week recovery period after the end of the dosing phase. Observations made in the first 16 days of the recovery period showed reversibility of some PF-05212384-related effects, as described below. PF-05212384 was generally tolerated after IV infusions up to 5 mg/kg per cycle in rats and dogs.

In the 3-cycle study in rats, 2 animals died after the first dose of 25 mg/kg. In the 8-cycle study in rats, no adverse effects were observed in rats given ≤5 mg/kg PF-05212384 per cycle. In the 8-cycle rat study, testicular tubular degeneration, adverse weight loss (correlated with decreased food consumption), and focal ulcerations of the skin were observed in rats given 10 mg/kg per cycle; in addition, 1 rat given 10 mg/kg per cycle was euthanized because of a progressively worsening focal ulceration at the junction of the tail and body. The 16-day recovery data in rats given 10 mg/kg per cycle showed reversibility of the PF-05212384-related weight loss and food consumption decreases, and focal lesions on the tail resolved in 3 of 4 rats by recovery day 16. In the 8-cycle toxicity study in dogs, adverse testicular tubular degeneration was observed at all dosages (0.5, 1.5, and 5 mg/kg per cycle). In dogs given 5 mg/kg per cycle, adverse weight loss, ulcerations in the oral mucosa, and decreases in thymic cellularity were observed. During the first 16 days of the recovery period, there was evidence of reversibility of weight changes in dogs given 5 mg/kg per cycle, and the PF-05212384-related oral ulcerations were resolved. Apart from the observations of adverse testicular tubular degeneration, the highest dose in the 8-cycle study that did not cause any severe, irreversible toxicity in dogs was 5 mg/kg per cycle. Safety updates will be provided on antemortem evaluations and observations and clinical and anatomic pathology evaluations from the recovery periods of the 8-cycle toxicity studies in rats and dogs.

1.3.2 Nonclinical Safety Pharmacology

Single-dose safety pharmacology studies in male rats infused with 0, 5, or 15 mg/kg indicated that PF-05212384 had no effects on central nervous system (CNS) function at the highest dose tested and had no effects on the respiratory system at the 5-mg/kg dose. Administration of 15 mg/kg PF-05212384, the highest dosage tested and a dosage 3 times greater than the maximum tolerated dose (5 mg/kg) in rats after 3 doses (1 dose/4 days), was associated with adverse decreases in respiratory rate and/or tidal volume, resulting in decreases in mean minute volume of 174 mL/minute (-23%), 132 mL/minute (-37%), 160 mL/minute (-25%), and 177 mL/minute (-24%) compared with vehicle control values at the 0.25-, 3-, 6-, and 24-hour post-dose assessments, respectively. These values were below the mean historical control range of 205 to 339 mL/minute. No statistically significant decreases in minute volume were observed at 48- or 72-hour post-dose assessments. Based on the magnitude and duration of the decreases in minute volume at 15 mg/kg, the decreased respiratory values were considered to be adverse. A cardiovascular study in male and female beagle dogs showed statistically significant adverse elevations in heart rate and arterial blood pressure at IV doses of 5 mg/kg but not at 0.5 or 1.5 mg/kg. The study found no effects at any dose on electrocardiogram (ECG) parameters, including corrected QT (QTc) interval prolongation or shortening, abnormal morphologic waveform changes, or abnormal atrial or ventricular arrhythmias. Additionally, results of a human ether-à-go-go related gene (hERG) assay indicated that PF-05212384 did not produce any inhibition of the hERG potassium ion current at concentrations up to 3 μM (1847.1 ng/mL).

1.3.3 Nonclinical Pharmacology

1.3.3.1 Brief Summary

The PI3K discovery project identified PF-05212384 in enzyme assays that measured activity of class I PI3Ks and mTOR. PF-05212384 is an ATP-competitive, triazine-scaffold compound that

is a pan class I PI3K inhibitor with a 0.4 nM IC50 against PI3K-α. Mutant forms of PI3K-α reported to have elevated lipid kinase activity [Carson et al, 2008] were inhibited by PF-05212384 at concentrations (IC50 = 0.6 to 0.8 nM) equivalent to those effective on wild type (wt) PI3K-α. The class I PI3K β, δ, and γ (gamma) □enzyme isoforms were inhibited at PF-05212384 concentrations 15- to 20-fold higher than that of PI3K-α, suggesting a small degree of selectivity. The mTOR kinase inhibition by PF-05212384 (IC50=1 nM) indicated that this compound was essentially an equipotent PI3K and mTOR inhibitor. Further characterization of PF-05212384 against a panel of 236 human protein kinases (Invitrogen) confirmed that PF-05212384 was a highly selective and potent inhibitor of class I PI3Ks and mTOR (RPT-76671). In this panel only Frap1 (mTOR) and B-Raf (wt and V600E mutant) were inhibited by PF-05212384 (RPT-76671). Subsequent IC50 values of 10 μM were determined for PF-05212384 versus both B-Raf enzymes. The IC50 values for PF-05212384 against all other kinases in the Invitrogen 236 panel were >1 μM (RPT-76671). Additionally, PF-05212384 was tested in house against the PIKKs ATR and SMG-1, and respective IC50 values were >10,000 nM and 5 nM. PF-05212384 inhibited the lipid kinase activity of class I PI3Ks and also the S/T kinase activity of mTOR. Class I PI3Ks convert phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3) at the inner cell membrane [Engelman , 2006; Shaw & Cantley, 2006]. PIP3 is bound by the pleckstrin homology (PH) domains of both PDK1 and Akt S/T kinases resulting in their close proximity at the inner cell membrane where PDK1 phosphorylates (at T308) and activates Akt [Alessi, 1997]. In lieu of directly monitoring cellular PIP3 levels, PF-05212384 inhibition of PI3K was demonstrated by potent (IC_{50} <30 nM) suppression of Akt phosphorylation at T308. Full activation of Akt kinase occurs when the mTOR containing target of rapamycin complex (TORC)-2 protein complex phosphorylates Akt at the S473 site [Sarbassov, 2005]. Potent (IC_{50} <30 nM) suppression of Akt phosphorylation at S473 was also caused by PF-05212384. PF-05212384 did not affect the overall Akt content in MDA361 cells, indicating phospho-Akt (pAkt) suppression was a not an artifact of nonspecific compound cytotoxicity. Both of the mTOR kinase containing protein complexes, TORC1 and TORC2, were inhibited by PF-05212384. An example of PF-05212384 effect on TORC1 is suppression of 4EBP1 phosphorylation by the TORC1 protein complex. Cap-dependent protein translation is controlled by 4EBP1 [Gingras, 1998]. TORC1 phosphorylation of 4EBP1 was inhibited at an IC_{50} concentration <30 nM. PF-05212384 suppression of Akt phosphorylation led to the consequent inhibition of phosphorylation of Akt effector proteins. Akt kinase regulates, by phosphorylation, a number of downstream effector proteins that in turn regulate protein synthesis, glucose metabolism, proliferation, angiogenesis, and cell survival [Altomare & Testa, 2005]. Examples of Akt effectors are: ENOS, which generates nitrous oxide in blood vessels and is involved in regulation of vascular function and angiogenesis [Fulton, 1999], and GSK-3, an serine/threonine protein kinase that regulates cell cycle progression and glucose metabolism [Cross, 1995]. Akt phosphorylation of ENOS on S1177 causes its activation, whereas Akt phosphorylation of S9/S21 of GSK-3α/GSK-3β inhibits their function [Fulton, 1999; Cross, 1995]. PF-05212384 potently suppressed the phosphorylation of both of these Akt effectors at IC_{50} concentrations <30 nM. Another PF-05212384 effect that was particularly evident in MDA361 cells was the induction of cleaved PARP. PARP is a protein involved in DNA repair and programmed cell death [Maira, 2008; Tewari, 1995]. PARP cleavage by caspase 3 facilitates cellular disassembly and serves as a marker of cells undergoing apoptosis [Maira, 2008; Tewari, 1995]. In tumor cells, PI3K pathway activation of Akt kinase inhibits the activation of various caspases (e.g., caspase 3) involved in programmed cell death (apoptosis). In MDA361, PF-05212384 suppression of Akt phosphorylation coincided with detectable cleaved

PARP at 30 nM PF-05212384, and increased amounts of cleaved PARP at concentrations ≥100 nM. Cleaved PARP was detected in MDA361 breast tumor cells exposed to PF-05212384 for as little as 1 hour (at ≥100 nM PF-05212384) (RPT-76671), and 24-hour exposure of MDA361 to ≥300 nM PF-05212384 caused overt cell death in >50% of cells. The potency of PF-05212384 to inhibit Akt phosphorylation and induce cleaved PARP in MDA361 was compared to an advanced (phase 2) PI3K/mTOR inhibitor (WYE-125739, BEZ235 Novartis) [Maira, 2008] and also to a highly selective mTOR kinase inhibitor (WYE-125132, with IC_{50} against mTOR=0.3 nM; IC_{50} against PI3K-α = 1 μM). WYE-125132, the selective mTOR inhibitor, did not affect Akt phosphorylation at T308 (as expected), and all three compounds suppressed Akt phosphorylation at S473 (as expected). Suppression of Akt phosphorylation at T308 demonstrates compound effect on PI3K activity, whereas suppression of Akt phosphorylation at S473 signifies compound effect on the TORC2 kinase complex.

1.3.3.2 Safety Pharmacology

The safety pharmacology studies included in this section were conducted by Wyeth and/or its contractor under Good Laboratory Practice (GLP) regulations. Quality Assurance Statements and compliance information can be found in the reports for these studies. For studies with audited reports, there were no known deviations or omissions that affected the quality or integrity of the data. The safety pharmacology of PF-05212384 was characterized for the central nervous system (CNS) and respiratory system in male rats, and for the cardiovascular system in an in vitro human ether-à-go-go related gene (hERG) potassium ion channel assay and in vivo in male and female dogs. These studies are summarized below.

1.3.3.3 Central Nervous System

PF-05212384 was administered to male Sprague-Dawley (S-D) rats (8/group) as a single 5-minute IV infusion dosage of 0, 5, or 15 mg/kg, based on a dose volume of 5 mL/kg (RPT-76759). The control group received the vehicle consisting of 0.3% L-lactic acid, 5% D-mannitol, sterile water for injection, and 1 N sodium hydroxide for pH adjustment. The control dosing formulation also contained 5% dextrose for injection. CNS function was evaluated using a functional observational battery (FOB), measurement of forelimb and hind limb grip strength, and measurement of rectal temperature. These evaluations were conducted approximately 24 hours before dosing and at 0.25, 3, 6, 24, 48, and 72 hours after dosing to ensure that the potential effects of PF-05212384 were evaluated across a range of plasma test article concentrations based on current pharmacokinetic data (time to peak concentration [t_{max}] was at the termination of infusion, with an apparent elimination half-life [$t_{1/2}$] of 11.5 hours. Mortality, clinical condition, and body weights also were evaluated. Animals were euthanized after the last post-dose CNS evaluation. There were no PF-05212384-related effects on FOB parameters, grip strength, or rectal temperature for animals given 5 or 15 mg/kg, and there was no mortality or moribundity in this study. PF-05212384-related clinical signs included decreased feces (days 2 to 4) in the 15 mg/kg dosage group, and dose-dependent body-weight loss (day 1 to the 48-hour post-dose assessment) of 4% and 13% in the 5 and 15 mg/kg dosage groups, respectively. Body weight gain (2% to 4%) was observed in all dosage groups from days 3 to 4. In conclusion, PF-05212384 administered by 5-minute IV infusion to male rats as a single dosage of 0, 5, or 15 mg/kg did not produce any effects on CNS function. The NOEL for PF-05212384 on CNS function was 15 mg/kg, the highest dosage tested and a

dosage that is 3 times greater than the MTD (5 mg/kg) in rats after 3 doses (1 dose/4 days) of PF-05212384.

1.3.3.4 Respiratory System

PF-05212384 was administered to male Sprague-Dawley rats (8/group) as a single 5-minute IV infusion dosage of 0, 5, or 15 mg/kg, based on a dose volume of 5 mL/kg (RPT-76760). The control group received the vehicle consisting of 0.3% L-lactic acid, 5% D-mannitol, sterile water for injection, and 1 N sodium hydroxide for pH adjustment. The control dosing formulation also contained 5% dextrose for injection. Using head out plethysmography, respiratory rate and tidal volume were recorded approximately 24 hours before dosing and at approximately 0.25, 3, 6, 24, 48, and 72 hours after dosing. Minute volume was calculated. The timing of these respiratory evaluations was chosen to ensure that the potential effects of PF-05212384 were evaluated across a range of plasma test article concentrations based on current pharmacokinetic data (t_{max} was at the termination of infusion, with a $t_{1/2}$ of 11.5 hours). Mortality, clinical condition, and body weights also were evaluated. Animals were euthanized after the last post-dose respiratory system evaluation. There were no effects on respiratory function in animals given the vehicle control or 5 mg/kg dosage of PF-05212384, and there was no mortality or moribundity in this study. In animals given 15 mg/kg of PF-05212384, a dosage that is 3 times greater than the MTD (5 mg/kg) in rats after 3 doses (1 dose/4 days) of PF-05212384, there were statistically significant decreases in respiratory rate of 22%, 17%, and 25% compared with time-matched vehicle controls at the 3-, 6-, and 24-hour post-dose assessments, respectively. The mean values for respiratory rate at 15 mg/kg were 121, 128, and 143 breaths/minute at the 3-, 6-, and 24-hour post-dose assessments, respectively, and these values are below the mean historical control range (164 to 241 breaths/minute). There were no statistically significant decreases in respiratory rate at 15 mg/kg at the 48- or 72-hour post-dose assessments. A decrease in tidal volume of 20% compared with vehicle controls was observed at the 3-hour post-dose assessment in the 15 mg/kg dosage group. The mean value for tidal volume at 15 mg/kg was 1.10 mL at the 3-hour post-dose assessment, and this value is within the mean historical control range (1.06 to 1.66 mL). PF-05212384-related decreases in respiratory rate and tidal volume resulted in decreases in minute volume of 23%, 37%, 25%, and 24% compared with time-matched vehicle control values at the 0.25-, 3-, 6-, and 24-hour post-dose assessments, respectively. Decreases in minute volume from pre-dose values were 30%, 47%, 36%, and 29% at the 0.25-, 3-, 6-, and 24-hour post-dose assessments, respectively, compared with decreases in minute volume of 8%, 15%, 12%, and 5% in the vehicle-control group at the same time intervals. The mean values for minute volume at 15 mg/kg were 174, 132, 160, and 177 mL/minute at the 0.25-, 3-, 6-, and 24-hour post-dose assessments, respectively, and these values are below the mean historical control range (205 to 339 mL/minute). PF-05212384-related clinical signs included decreased feces (days 2 to 4) and hair shedding (days 3 and 4) in the 15 mg/kg dosage group, and dose-dependent body-weight loss (day 1 to the 48-hour post-dose assessment) of 3% and 11% in the 5 and 15 mg/kg dosage groups, respectively. Body-weight gain (2% to 5%) was observed in all dosage groups from days 3 to 4. In conclusion, PF-05212384 administered by 5-minute IV infusion to male rats as a single dosage of 0 or 5 mg/kg produced no effects on respiratory function. A single IV infusion dosage of 15 mg/kg, a dosage that is 3 times greater than the MTD (5 mg/kg) in rats after 3 doses (1 dose/4 days) of PF-05212384, produced decreases in respiratory rate, tidal volume, and minute volume at 0.25 to 24 hours after dose

administration. Based on these results, the NOEL for PF-05212384 on respiratory function was 5 mg/kg, when given as a single 5-minute IV infusion dosage to male rats.

1.3.3.5 Cardiovascular System

In Vitro hERG Potassium Ion Channel Assay

The potential effects of PF-05212384 on the rapidly activating delayed rectifier cardiac potassium ion current (IKr) were examined in the in vitro hERG potassium ion channel assay (RPT-76804). Human embryonic kidney (HEK)-293 cells that were stably transfected with hERG cDNA were studied at 33ºC to 35ºC ±2ºC using patch clamp electrophysiology techniques. The effect of PF-05212384 at concentrations of 1 µM (615.7 ng/mL, based on the molecular weight of the free base [615.7 g/mol]) and 3 µM (1847.1 ng/mL) on the hERG channel potassium ion current was evaluated. Testing of higher concentrations was not possible because of limited solubility of the test article. PF-05212384 did not produce inhibition of the hERG potassium ion current that was significantly ($p \leq 0.05$) different from the inhibition observed in cells exposed to vehicle alone. PF-05212384 did not produce any inhibition of the hERG potassium ion current at concentrations up to 3 µM (1847.1 ng/mL), the highest concentration that could be tested because of solubility limitations. Based on the results of this study, the IC_{50} is >3 µM (>1847.1 ng/mL).

Single-Dose Intravenous, Dogs

PF-05212384 was administered to male and female dogs (4/gender) as a single 5-minute IV infusion dosage of 0, 0.5, 1.5, and 5 mg/kg, at a dose volume of 10 mL/kg and according to a Latin-square crossover dosing paradigm (RPT-76613). Dosing was separated by a 1-week washout period. Body weights were obtained within 6 days before each day of dosing, for the purpose of calculating the dosage to be administered. One (1) female was removed from the study after the second dosing because of trauma to the left eye that occurred during the exercise period; the animal required systemic antibiotic treatment. Data collected for this animal during dosing periods 1 and 2 (days 1 and 8, respectively) were included in the statistical analysis, but there were no data collected for this animal during dosing periods 3 and 4 (days 15 and 22, respectively). The vehicle control stock formulation consisted of 0.3% L-lactic acid, 5% D-mannitol, and sterile water for injection. The control article dosing formulation was prepared by diluting control stock formulation with 5% dextrose for injection. Parameters collected using radiotelemetry consisted of arterial blood pressures (systolic, diastolic, and mean), heart rate, and lead II ECG. The telemetry data were collected for 60-second periods every 5 minutes, for 25 hours before and 48 hours after dosing with vehicle control or PF-05212384. Effects on heart rate and arterial blood pressure were evaluated at hourly intervals in all animals at all dosages from 1 to 48 hours after dosing. PR, QRS, and QT intervals of the ECG were measured from readable ECGs at 5-minute intervals from approximately 24 hours before to 48 hours after dosing using data from all animals at all dosages. Effects on the ECG were evaluated every 30 minutes (nominal) during the initial 2-hour post-dose period, a 2-hour period centered 18 hours after dose administration, and at time points of 7, 23, and 47 hours after dose administration to ensure characterization of potential PF-05212384 effects across a range of plasma test article concentrations based on current pharmacokinetic data (t_{max} was at the termination of infusion, with $t_{1/2}$ of 16.1 hours). Pre-dose ECGs were chosen to correspond with clock times approximately 24 hours before the post-dose time point evaluated. ECG recordings were also evaluated for rhythm disorders. Observations for clinical signs and mortality were performed at least once daily, beginning the day before the first

dose administration. Administration of PF-05212384 as a single 5-minute IV infusion dosage of 0.5 and 1.5 mg/kg to male and female dogs did not produce changes in heart rate or arterial blood pressure (systolic, diastolic, or mean). Administration of PF-05212384 as a single 5-minute IV infusion dosage of 5 mg/kg to male and female dogs resulted in a consistent, statistically significant average increase in mean heart rate of 24% (22 bpm) during the 12- to 33-hour post-dose period. In addition, a single 5-minute IV infusion dosage of 5 mg/kg of PF-05212384 produced statistically significant 7% (5.9 mm Hg), and 6% (6.6 mm Hg) or 5% (7.3 mm Hg), 12% (9.3 mm Hg), and 9% (8.6 mm Hg), respectively, during the initial 12-hour post-dose period or the 31- to 37-hour post-dose period, compared with vehicle control. There were no effects on the ECG parameters (PR, QRS, QT, and corrected QT [QTc] intervals), including no evidence of QTc prolongation or shortening, abnormal morphologic waveform changes, or abnormal atrial or ventricular arrhythmias, in any of the ECGs examined in animals after receiving the vehicle control or any dosage of PF-05212384. PR, QRS, and QTc intervals after administration of PF-05212384 were comparable with those values during the pre-dose period and after administration of vehicle control. There was no mortality or moribundity in this study. Clinical observations included single incidences of post-dose emesis after administration of the 0 (vehicle control), 0.5, and 1.5 mg/kg dosages, and an increased frequency (4 of 7 animals) of post-dose emesis after administration of the high dosage of 5 mg/kg of PF-05212384. Clinical observations of post-dose emesis in the cardiovascular safety pharmacology study were similar to clinical observations in the IV dose-ranging and toxicity studies in dogs. In conclusion, administration of single 5-minute IV infusion dosages of PF-05212384 to male and female beagle dogs produced no effects on heart rate or arterial blood pressure at 0.5 and 1.5 mg/kg, and produced consistent, statistically significant elevations in heart rate and arterial blood pressure at 5 mg/kg. Based on the magnitude and duration of change, the elevations in heart rate and arterial blood pressure after administration of the high dosage of 5 mg/kg of PF-05212384 were considered adverse. There were no effects on the ECG, including no evidence of QTc prolongation or shortening, abnormal morphologic waveform changes, or abnormal atrial or ventricular arrhythmias, at any dosage of PF-05212384 administered in this study. Based on these results, the NOEL in the cardiovascular safety pharmacology study was 1.5 mg/kg for hemodynamic effects and 5 mg/kg for ECG effects, when given as a single 5-minute IV infusion dosage to male and female dogs.

1.3.3.6 Exposure Comparisons

Blood samples for the determination of PF-05212384 concentrations were not collected in the CNS or respiratory safety pharmacology studies in male rats, or in the cardiovascular safety pharmacology study in dogs. However, data from 8-cycle (cycle = 1 dose/4 days) IV toxicity studies in rats and dogs are available. Exposures (peak concentration [C_{peak}] and AUC) after a single 5-minute IV infusion dosage in the 8-cycle (1 dose/4 days) repeat-dose toxicity studies were compared with the exposures (C_{peak} and AUC) at the MED in the MDA361 xenograft mouse model and with the predicted exposure (AUC) at the proposed clinical IV starting dose in the first-in-human, dose-escalation study. Exposure comparisons are described below.

CNS and Respiratory Safety Pharmacology

After a single 5-minute IV infusion dosage of 15 mg/kg in male rats, the highest dosage administered in the CNS safety pharmacology study, where no effects were observed, exposure (C_{peak} = 38,211 ng/mL and AUC = 20,277 ng•h/mL) was approximately 4.7 times the C_{peak} (8202

ng/mL) 2 and 7.1 times the AUC (2863 ng•h/mL) at the MED of 3 mg/kg in the MDA361 xenograft mouse model. At the highest dosage of 15 mg/kg in the NS safety pharmacology study, exposure (AUC) after a single 5-minute IV infusion dosage was approximately 8.6 times the predicted exposure at the proposed starting dose (10 mg; AUC = 2350 ng•h/mL) in the first-in-human clinical study. After a single 5-minute IV infusion dosage of 5 mg/kg in male rats, the dosage where no effects were observed in the respiratory system safety pharmacology study, exposure (Cpeak = 12,737 ng/mL and AUC = 6759 ng•h/mL) was approximately 1.6 times the Cpeak and 2.4 times the AUC at the MED in the MDA361 xenograft mouse model. Exposure (AUC) after a single 5-minute IV infusion dosage of 5 mg/kg in male rats was approximately 2.9 times the predicted exposure at the proposed starting dose (10 mg) in the first-in-human clinical study.

Cardiovascular Safety Pharmacology

PF-05212384 did not produce inhibition of the hERG potassium ion channel current at concentrations up to 3 μM (1847.1 ng/mL). It is common practice to calculate the exposure ratio comparing the IC_{50} concentration in the hERG assay to the free fraction (non-protein bound) of the efficacious C_{peak} [Redfern, 2003] because the perfusion medium (HEPES physiological salt solution) used in the in vitro hERG assay is a protein-free solution; thus, no protein binding takes place. Since the inhibition (0.2%) at the highest concentration tested (3 μM) was similar to the vehicle control, the IC50 was not calculated, but was >3 μM. Therefore, the exposure ratio was calculated based on the highest concentration tested in the hERG assay (3 μM; 1847.1 ng/mL), where there was no inhibition, and the free fraction (non-protein bound) of the efficacious C_{peak}. At the MED (3 mg/kg) in the MDA361 xenograft mouse model, the C_{peak} is 8202 ng/mL. Mean percent protein binding in mouse plasma is 94.6%, leaving 5.4% unbound to plasma proteins (or free). Therefore, the highest concentration of PF-05212384 that could be tested in the hERG assay (3 μM; 1847.1 ng/mL), where there was no inhibition, is 4.2 times greater than the free fraction of the efficacious C_{peak} (443 ng/mL) in the MDA361 xenograft mouse model. After a single 5-minute IV infusion dosage of 1.5 mg/kg in male and female dogs, the NOEL for effects on heart rate and arterial blood pressure in the cardiovascular safety pharmacology study, exposure (C_{peak} = 5665 ng/mL and AUC = 3472 ng•h/mL; average of male and female values for the C_{peak} and AUC) was approximately 0.7 times the C_{peak} and 1.2 times the AUC at the MED in the MDA361 xenograft mouse model. Exposure (AUC) after a single 5-minute IV infusion dosage of 1.5 mg/kg in male and female dogs was approximately 1.5 times the predicted exposure at the proposed starting dose (10 mg) in the first-in-human clinical study. After a single 5-minute IV infusion dosage of 5 mg/kg in male and female dogs, the highest dosage administered in the cardiovascular safety pharmacology study, where no ECG effects were observed, exposure (C_{peak} = 24,492 ng/mL and AUC = 14,934 ng•h/mL; average of male and female values for the C_{peak} and AUC) was approximately 3.0 times the C_{peak} and 5.2 times the AUC at the MED in the MDA361 xenograft mouse model. Exposure (AUC) after a single 5-minute IV infusion dosage of 5 mg/kg in male and female dogs was approximately 6.4 times the predicted exposure at the proposed starting dose (10 mg) in the first-in-human clinical study.

1.4 **Effects in Humans**

The clinical studies conducted to date on PF-05212384 (gedatolisib, Pfizer) have been conducted in accordance with the United States Food and Drug Administration (US FDA), Good Clinical Practice (GCP) regulations and EU Directive on GCP. Study designs and parameters evaluated are

consistent with accepted principles and practices as outlined in International Conference on Harmonization (ICH) guidelines. The studies are summarized briefly from the most recent version of the Investigator Brochure (IB) of September 2015, and reflect all data obtained prior to the cutoff date of 30 April 2015.

As of 30 April 2015, the clinical database includes information on a total of 302 patients with solid tumors who have received PF-05212384 in 7 clinical trials. Of the 302 patients, 129 were treated with PF-05212384 as a single agent in clinical trials B2151001, B1271004 and B2151006. The remaining 173 patients received PF-05212384 in combination with other anti-cancer agents in clinical trials B1271002, B2151002, B2151005, and B2151007. The clinical safety data reported in the following sections are based on available data as of the data cutoff date.

Completed Studies:

Phase 1 Study B2151001

B2151001 is a completed Phase 1, open-label, dose-escalation first-in patient (FIP) study of single-agent PF-05212384 in patients with advanced solid tumors. The primary objective of Part 1 of the study was to determine the safety, tolerability, and maximum-tolerated dose (MTD) of single-agent PF-05212384 administered once weekly (QW) as an intravenous (IV) infusion; secondary objectives included assessing pharmacokinetic (PK) parameters of PF-05212384, evaluating pharmacodynamic (PD) markers for target inhibition, and assessing preliminary antitumor activity. Part 2 of the study was conducted in patients with selected tumor types that, based on nonclinical considerations, are thought to be sensitive to the PI3K pathway inhibition. The primary objectives of Part 2 of the study were to gather additional safety information at the MTD and assess preliminary antitumor activity; secondary objectives included assessing PK parameters of PF-05212384 and evaluating PD markers for target inhibition. In this study, PF-05212384 was administered to 77 patients with advanced solid tumors. Doses administered ranged from 10 to 319 mg. A dose level of 154 mg IV QW (n = 42) was defined as the MTD of single agent PF-05212384.

At the MTD (154 mg) of single-agent PF-05212384, the 3 most frequently experienced Adverse Events (AEs; all grades) at the PF-05212384 154 mg dose level were mucosal inflammation/stomatitis, nausea, and decreased appetite (experienced by 57.1% [24/42], 54.8% [23/42], and 38.1% [16/42] of patients, respectively); the majority were Grade 1 AEs (Grade 1 inflammation/stomatitis, nausea, and decreased appetite experienced by 47.6% [20/42], 45.2% [19/42], and 26.2% [11/42] of patients, respectively). The most frequent (≥3 patients) Grade 3 all-causality AEs included alanine aminotransferase (ALT) increased and asthenia (4 [9.5%] patients and 3 [7.1%] patients, respectively); no other Grade 3 AE was reported in more than 2 patients. Grade 4 all-causality AEs included hyperbilirubinemia and pulmonary embolism (1 patient each). Five (5) patients experienced in total seven Grade 5 all-causality AEs which included disease progression (3 patients) and aortic disorder, colonic obstruction, gastrointestinal stromal tumor, and intestinal obstruction (1 patient each). At the MTD (154 mg) of single-agent PF-05212384, the most frequent (≥20%) laboratory abnormalities (worst grade on study, all cycles) were anemia (81.0%), hyperglycemia (78.6%), creatinine increased (71.4%), prothrombin time prolongation (64.9%), lymphopenia (absolute; 62.5%), alkaline phosphatase increased (61.9%), aspartate aminotransferase (AST) increased (59.5%), ALT increased (47.6%), hypoalbuminemia (45.2%),

hypomagnesemia (42.9%), urine protein (41.2%), hyponatremia (40.5%), partial thromboplastin time (37.8%), hypokalemia (31.0%), prothrombin time/International Normalization Ratio (28.9%), hypocalcemia (28.6%), leukocytopenia (28.6%), hyperbilirubinemia (23.8%), and thrombocytopenia (20.0%).

Phase 2 Study B1271004

B1271004 is a completed Phase 2, open-label, 4-arm, optimal Simon 2 stage non-comparative, multi-center study to assess the safety, efficacy, PK, and PD of PF-04691502 (an oral PI3K/mTOR inhibitor) and PF-05212384 (an IV PI3K/mTOR inhibitor). This study was conducted in adult female patients with recurrent endometrial cancer for whom no standard therapy is available. The study was initially 4-arms, although on 09 October 2012, Pfizer decided to discontinue the clinical development of PF-04691502 and stop further enrollment of patients into study Arms A and C.

Subjects were stratified by Stathmin status (high or low, which represents activated or basal PI3K, respectively) during screening. The primary efficacy endpoint is the clinical benefit rate (at 16 weeks). In a lead-in cohort (LIC), single-agent PF-05212384 at the MTD identified in the FIP study was found to be safe and tolerable in Japanese patients (n = 6). Clinical sites in Japan also enrolled patients into Arms A and D. Enrollment to B1271004 was discontinued on 23 January 2014 following a strategic decision based on the lack of sufficient efficacy. As of the data cutoff date 30 April 2014 (last patient study completion date), based on data entered into the clinical database, a total of 46 patients (6 patients in the Japan LIC and 40 patients in Phase 2) were treated with PF-05212384 in the study.

Phase 2 Study B2151005

B2151005 is a completed Phase 2, randomized, open-label, 2-arm, multi-center study in patients with metastatic colorectal cancer (mCRC), including a LIC in Japanese patients. The primary objective of the study is to investigate whether PF-05212384 in combination with irinotecan is superior to cetuximab in combination with irinotecan in prolonging progression-free survival (PFS) in patients with KRAS and NRAS wild type mCRC who have progressed following prior treatment with irinotecan, oxaliplatin, and fluoropyrimidines. The study is also designed to confirm the tolerability of the recommended Phase 2 dose (RP2D) of PF-05212384 in combination with irinotecan in Japanese patients. As of the data cutoff date 30 April 2015, based on data entered into the clinical database, 19 patients have been treated in B2151005. Thirteen (13) of these patients have been treated with PF-05212384 in combination with irinotecan (6 out of 13 were in the Japan LIC) and 6 patients were randomized to the non-PF-05212384 containing treatment arm in the Phase 2 portion of the study.

Phase 1 Study B2151006

B2151006 is a completed Phase 1, open-label, single-radio-labeled dose study to investigate the metabolism and excretion of [^{14}C] PF-05212384 in healthy male volunteers. The aim of the study is to investigate the metabolism, and excretion of [^{14}C]-PF-05212384, to characterize plasma, fecal, and urinary (if necessary) radioactivity and to identify any circulating or excreted metabolites, if possible, following a single 89 mg dose of [^{14}C]PF-05212384. The study was conducted in 6 healthy men and study was completed on 11 August 2014. A single IV infusion of PF-05212384 at a dose of 89 mg was well tolerated in healthy subjects evaluated in this study.

Phase 1b/2 Study B2151007

B2151007 is a completed Phase 1b/2, randomized, open-label, 2-arm, multi-center study in patients with mCRC, including a LIC in Japanese patients. The primary objective of the Phase 1b portion of the study is to assess safety and to determine the MTD and RP2D of PF-05212384 in combination with FOLFIRI in patients treated at non-Japanese clinical sites. The primary objective of the Phase 2 portion is to demonstrate that PF-05212384 in combination with FOLFIRI is superior to bevacizumab in combination with FOLFIRI in prolonging PFS in patients with mCRC who have progressed on a prior oxaliplatin containing regimen. The study is also designed to confirm the tolerability of the RP2D of PF-05212384 in combination with FOLFIRI in Japanese patients. As of the data cutoff date 30 April 2015, based on data entered into the clinical database, 17 patients have been treated with PF-05212384 in combination with fluorouracil/leucovorin/irinotecan (FOLFIRI) in the study.

Ongoing Studies:

Phase 1b Study B1271002

B1271002 is an ongoing Phase 1b, open-label, multiple center, dose-escalation study of PF-05212384 in combination with irinotecan and PF-05212384 in combination with PD-0325901 (an oral MEK inhibitor) in patients with advanced solid tumors. The primary objective of the study is to assess the safety and tolerability and to define the MTD of PF-05212384 in combination with irinotecan and PF-05212384 in combination with PD-0325901. This study is being conducted in parallel arms of sequential patient cohorts using a classical 3+3 study design (PF-05212384 in combination with irinotecan) and a zone (modified 3+3) design (PF-05212384 in combination with PD-0325901). For PF-05212384 in combination with irinotecan, a dose level of 110 mg weekly of PF-05212384 in combination with 180 mg/m2 administered every 2 weeks of irinotecan was defined as the MTD of this combination regimen. As of 30 April 2015, based on data entered into the clinical database, 44 patients with advanced cancers have been treated with PF-05212384 in combination with irinotecan and 36 patients with solid tumors containing KRAS or BRAF mutations have been treated with PF-05212384 in combination with PD-0325901, an oral inhibitor of MEK.

Phase 1 Study B2151002

B2151002 is an ongoing Phase 1b, open-label, 3-arm, dose-escalation, multi-center study in patients with advanced solid tumors. The primary objective of the study is to investigate the safety, tolerability, PK, and PD of PF-05212384 in combination with docetaxel, cisplatin, or dacomitinib. Successive cohorts of patients will receive selected doses of PF-05212384 in combination with selected doses of chemotherapeutic agents (docetaxel and cisplatin) or dacomitinib in 3 independent arms on an outpatient basis. As of the data cutoff date 30 April 2015, based on data entered into the clinical database, patients have been treated with PF-05212384 in combination with cisplatin (n = 16), dacomitinib (n = 28), and docetaxel (n = 19) in Study B2151002.

Investigator Initiated Research Studies

Three (3) Investigator initiated research (IIR) studies (WI179493, WI174764, and WI179849) are being conducted with PF-05212384. Due to the limited clinical data available regarding the IIR

studies as of the data cutoff date of 30 April 2015, detailed information regarding these studies would be provided as part of the next IB update.

Notably, in an ongoing trial of gedatolisib in combination with cisplatin-based chemotherapy, the presumed MTD has been safely exceeded, and patients have been accrued at a dose of 215 mg/week, though some patients have required a dose reduction to 180 mg/m2/week (personal communication with T. Manali, MD, Pfizer, Inc., 8/8/2016).

1.4.1 **Pharmacokinetics and Product Metabolism in Humans**

Final analysis of the pharmacokinetic data from B2151001 with single-agent PF-05212384 suggested that following 30-minute intravenous (IV) infusion doses, plasma PF-05212384 concentrations declined very rapidly in the first hours, followed by a slower decline with a terminal phase half-life (t½) of about 35 hours. Maximum plasma concentrations (end of infusion) and total exposure (AUC) appeared to increase proportionally with dose over the 10-mg to 319-mg dose range studied following both single-dose and multiple-dose administration. No drug accumulation was noted with once-weekly dosing. Study B2151006 titled "A Phase One, Open-Label Single-Radiolabeled Dose Study to Investigate the Metabolism and Excretion of [^{14}C]PF-05212384 in Healthy Male Volunteers" was conducted. After administration of [^{14}C]PF-05212384 to 6 male human subjects, 11.53%-14.75% of administered radioactivity was excreted in the urine and 66.43%-73.04% of administered radioactivity was recovered in the feces. The total recovery (urine + feces) from each of the subjects was in the range 80.45%-85.07% of administered radioactivity. Peak plasma concentrations for both total radioactivity and unchanged PF-05212384 were observed at the end of the 30-minute infusion. Based on ratios of PF-05212384 to total radioactivity for maximum observed concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUCinf), unchanged PF-05212384 accounted for about 82% of the peak radioactivity and 70% of the total radioactivity in plasma. The t½ for plasma PF-05212384 was 37 h while the apparent t½ for total radioactivity was 126 h. Metabolism of PF-05212384 was trace with the only identified metabolite being M5 in feces representing a mean of 0.4% of the total dose. Two additional unknown metabolites were observed in urine representing a mean of 0.2% and 0.3% of the total dose. A single IV infusion of PF-05212384 at a dose of 89 mg was well tolerated in healthy subjects evaluated in this study.

1.4.2 **Bioavailability**

A bioavailability study has not been performed. PF-05212384 is not evident in plasma following oral administration in animals.

1.4.2.1 **Population Subgroups**

Hepatically-Impaired Patients
The effects of hepatic impairment on multiple-dose PF-05212384 pharmacokinetics are unknown.

Renally-Impaired Patients
The effects of renal impairment on multiple-dose PF-05212384 pharmacokinetics are unknown.

1.4.3 **Pharmacokinetics in Patients**

Patients in Phase 2/3
It is currently unknown whether differences exist in the pharmacokinetic profile of PF-05212384 between patients and healthy volunteers.

Pharmacokinetics in Asian and Japanese Patients
It is currently unknown whether differences exist in the pharmacokinetic profile of PF-05212384 between Asian (including Japanese patients) and non-Asian patients.

1.4.4 **Drug-Drug Interactions**

In vitro studies in human microsomes and hepatocytes showed that there was minimal metabolism of PF-05212384 in all species, including human. No drug-drug interaction assessments with PF-05212384 have been performed in humans in vivo. However, based on the 50% inhibitive concentration (IC50) values determined from in vitro data for the different cytochrome P450s (CYPs) and the observed human plasma drug concentrations from Phase 1 Study B2151001, PF-05212384 is not likely to inhibit the metabolic clearance of concomitant drugs that are substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Although PF-05212384 inhibited CYP2C8 (IC50 value: 38 microM), it is unlikely that drug-drug interactions involving PF-05212384 and co-administered drugs that are substrates of CYP2C8 may occur, based on the observed Cmax levels from Phase 1 Study B2151001. Based on in vitro data, PF-05212384 may be considered a P-glycoprotein (P-gp) substrate, but based on findings from Phase 1 Study B2151001 it is not considered likely to affect the pharmacokinetics and disposition of concomitant drugs that are P-gp substrates.

Other Clinical Pharmacology Data
Pharmacokinetic/pharmacodynamic relationships between plasma levels of PF-05212384 and efficacy or tolerability are unknown.

1.4.5 **Safety**

Safety
Adverse events (AEs) are coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of the treatment emergent AEs (TEAEs) are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

1.4.5.1 **Single Agent PF-05212384 Studies**

Phase 1 (First-in-Patient) Study B2151001 of Single Agent PF-05212384 in Patients with Advanced Solid Tumors

Study Design
B2151001 is a completed Phase 1, first-in-patient (FIP), open-label, dose-escalation study of single-agent PF-05212384 in patients with advanced solid tumors. The primary objective of Part

1 of the study was to determine the safety, tolerability, and maximum tolerated dose (MTD) of single-agent PF-05212384 administered once weekly (QW) as an intravenous (IV) infusion; secondary objectives included assessing pharmacokinetic (PK) parameters of PF-05212384, evaluating pharmacodynamic (PD) markers for target inhibition, and assessing preliminary antitumor activity. Part 2 of the study was conducted in patients with selected tumor types with nonclinical features suggestive of higher sensitivity to PI3K/mTOR inhibition. The primary objectives of Part 2 of the study were to gather additional safety information at the MTD and assess preliminary antitumor activity; secondary objectives included assessing PK parameters of PF-05212384 and evaluating PD markers for target inhibition. Patients were enrolled and dosed according to a modified continual reassessment method (CRM) targeting a 25% Dose Limiting Toxicity (DLT) rate for the MTD estimation phase of the trial. Patients were enrolled in cohorts of 2 to 4 patients, starting with 10 mg for the first cohort. The possible doses explored were identified from a fine grid of doses ranging from 10 mg to 319 mg. Starting in the second cohort, patients were assigned to a dose that was closest to the MTD prediction based on the CRM. The above model was updated after completion of each cohort's DLT period. To prevent overly aggressive dose-escalation, the maximum allowed dose increase from the highest dose that was previously studied was limited to 4 increments at a time, (ie, no more than 107% dose increase at a time). In this study, PF-05212384 was administered to 77 patients with advanced solid tumors. Doses administered ranged from 10 mg to 319 mg. A dose level of 154 mg administered QW (n = 42) was defined as the MTD of single agent PF-05212384.

Dose-Limiting Toxicities

DLTs were only observed at or above a PF-05212384 dose of 154 mg QW (ie, at or above the estimated MTD). Twelve patients experienced a total of 13 DLTs (PF-05212384 154 mg: 2 of 42 [4.8%] patients; PF-05212384 222 mg: 5 of 7 [71.4%] patients; PF-05212384 266 mg: 3 of 8 [37.5%] patients; and PF-05212384 319 mg: 2 of 4 [50.0%] patients). The most frequently reported DLT was mucosal inflammation (6 of 13 DLTs); an additional patient experienced a DLT of stomatitis. Each of the DLTs occurred during the active treatment phase, had an onset during Cycle 1, and was considered by the Investigator to be treatment-related.

Treatment-Emergent All-Causality Adverse Events

At the 154 mg PF-05212384 dose level. The 3 most frequently experienced AEs at this dose level were nausea, mucosal inflammation, and decreased appetite experienced by 54.8% [23/42], 45.2% [19/42], and 38.1% [16/42] of patients, respectively. Grade 1 nausea, mucosal inflammation, and decreased appetite were experienced by 45.2% [19/42], 38.1% [16/42], and 26.2% [11/42] of patients, respectively. Overall, 11.9% (5/42) of patients experienced an AE of stomatitis, of which 9.5% were Grade 1 AEs.

Discontinuations Due to Adverse Events

Overall, 10 patients were discontinued due to AEs (PF-05212384 10 mg, 1 patient; 89 mg, 1 patient; 154 mg, 5 patients; 222 mg, 2 patients; and 319 mg, 1 patient). Three patients were discontinued due to treatment-related AEs; 2 patients discontinued at the PF-05212384 222 mg dose level, 1 patient due to mucosal inflammation and 1 patient due to elevated alanine aminotransferase, and 1 patient discontinued at the PF-05212384 319 mg dose level due to mucosal inflammation.

Serious Adverse Events

Of all-causality SAEs in the Phase 1 (FIP) study B2151001 at doses approximating the MTD and above, the most frequent all-causality SAE at the MTD (154 mg) was disease progression, reported in 7.1% (3/42) of patients, followed by pain, reported 4.8% (2/42) of patients. No other SAEs were experienced by >1 patient at the MTD. Two patients (1 patient [10020220] treated with 154 mg PF-05212384 and 1 patient [10020208] treated with 319 mg PF-05212384) experienced a treatment-related SAE of mucosal inflammation. One patient (10050110) treated with 266 mg PF-05212384 experienced a treatment-related SAE of hyperglycemia. One patient (10010152) who received a starting dose of 319 mg PF-05212384 and was dose reduced to 239 mg PF-05212384 at Cycle 4 day 22 due to toxicity, experienced treatment-related SAEs of abdominal pain, vomiting and diarrhea at the reduced dose.

Deaths

In the Phase 1 (FIP) study B2151001, nine patients died on treatment or within 28 days of the last dose of study drug, 1 patient (10030302) died post study treatment (>28 days after the last dose of study drug), and 1 patient (10010014) died prior to the start of treatment. The most frequently reported event with a fatal outcome was disease progression (7 patients). Note that patients could have experienced more than 1 event with a fatal outcome. None of the deaths were considered to be related to treatment.

Phase 2 Study B1271004 of Single Agent PF-05212384 in Patients with Advanced Endometrial Cancer

Study Design

B1271004 is an ongoing Phase 2, randomized open label, two-stage study of single agent PF-05212384 at a dose of 154 mg IV QW in patients with recurrent endometrial cancer. Subjects are stratified by Stathmin status (high or low which was thought to represent activated or basal PI3K, respectively) during screening. A lead-in cohort (LIC) is also included to determine if single agent PF-05212384 is safe and tolerable in Japanese patients. The primary efficacy endpoint of the study is clinical benefit rate (at 16 weeks). As of the data cutoff date of 30 April 2015, 40 patients were enrolled into the Phase 2 portion (all in Stage 1) of the study and 6 patients were enrolled into the LIC in Japan. In the LIC for Japanese patients, 2 dose levels of PF-05212384 (89 and 154 mg IV QW) were tested in 3 patients per dose.

Dose-Limiting Toxicities

No formal analysis of DLTs was conducted in the study. In the Japan LIC, one patient who received 154 mg of PF-05212384 experienced unacceptable toxicity (Grade 3 maculopapular rash) during Cycle 1.

Treatment-Emergent All-Causality Adverse Events

At the 154 mg PF-05212384 dose level, the most frequently experienced AEs at this dose level were nausea, mucosal inflammation, diarrhea, and decreased appetite experienced by 55.0% [22/40], 50.0% [20/40], 45.0% [18/40], and 42.5% [17/40] of patients, respectively. These toxicities were all Grade 1 or 2 except for 4 patients (10.0%) with fatigue, 3 patients (7.5%) each with diarrhea and hypertension, 2 patients each with Asthenia, urinary tract infection and dyspnea, and 1 patient each with stomatitis, abdominal pain, aphthous stomatitis, large intestinal

obstruction, rectal hemorrhage, mucosal inflammation, disease progression, pain, hypomagnesaemia, diabetes mellitus, hypercholesterolemia, hypokalemia, hyponatremia, bacteriuria, lung infection, pyelonephritis, respiratory tract infection, cerebrovascular accident, oropharyngeal pain, pulmonary embolism, arthralgia, back pain, fistula, hematuria, proteinuria, urinary tract obstruction, vascular access complication, anemia, gastric cancer, and cardiac failure experienced Grade 3 AEs. Grade 4 events were observed in 1 patient each with pulmonary embolism and blood creatinine increased.

Discontinuations Due to Adverse Events
As of the data cutoff date of 30 April 2015, in the Phase 2 portion of the study, 5 patients discontinued due to AEs which was considered by the Investigator to be related to treatment. The events included pulmonary embolism in 2 patients and infusion related reaction, fatigue, and rigors in one patient each. As of the data cutoff date of 30 April 2015, in the Japan LIC, no patients discontinued due to an AE; 6 patients discontinued due to disease progression.

Serious Adverse Events
The highest numbers of all-causality-SAEs were large intestinal obstruction and urinary tract infection (5 events each) and disease progression (3 events).

Deaths
As of the 30 April 2015 cutoff date, 2 patients died on study (on treatment or within 28 days after last dose); all due to disease progression.

Laboratory Abnormalities
Most of the hematology test abnormalities were Grades 1 or 2. Grade 4 hematology test abnormalities were reported for platelets, white blood cells and lymphopenia (1 of 40 [2.5%] patient each). Most of the chemistry test abnormalities were Grades 1 or 2. Grade 4 chemistry test abnormalities were reported for hyponatremia (1 of 40 [2.5%] patient) and hypocalcemia (2 of 40 [5.0%] patients).

PF-05212384 Single Agent Pooled Safety Data Generated in B1271004 and B2151001
The pooled safety data includes data from the 42 patients treated in B2151001 and 40 patients treated in the phase 2 portion of B1271004 who received PF-05212384 at a dose of 154 mg IV weekly. The 3 most frequently experienced AEs at this dose level were nausea, mucosal inflammation, and decreased appetite experienced by 54.9%, 47.6%, and 40.2% of patients, respectively.

1.4.5.2 PF-05212384 Combination Studies

Phase 1b Study B1271002 of PF-05212384 in Combination with Irinotecan and PF-05212384 in Combination with PD-0325901 in Patients with Advanced Solid Tumors
B1271002 is an ongoing Phase 1b, open-label, double-arm, multicenter, dose-escalation, study of PF-05212384 in combination with irinotecan and PF-05212384 in combination with PD-0325901 (an oral MEK inhibitor) in patients with advanced solid tumors. The primary objective of the study is to assess safety and tolerability and define the MTD of PF-05212384 in combination with

irinotecan (Arm C) and PF-05212384 in combination with PD-0325901 (Arm D). Arm C of the study is being conducted in parallel arms of sequential dose levels using a classical 3+3 study design. In Arm C, successive cohorts of patients received escalating doses of PF-05212384 (starting dose of 95 mg QW) in combination with irinotecan (180 mg/m2 every 2 weeks [Q2W]). The MTD was defined as 110 mg QW of PF-05212384 and enrollment of 20 patients with colorectal cancer and 10 patients with pancreatic cancer in the expansion cohort was started. Arm D is being conducted with a zone design, which consists of a modified 3+3 design that allows opening more than one dose level at the same time. In Arm D, patients receive escalating doses of PF-05212384 (starting dose of 110 mg QW with a maximum planned dose level of PF-05212384 of 130 mg QW) in combination with PD-0325901 (starting dose from 2 mg BID 3 weeks on/1 week off with the possibility to increase the dose to 4 and 6 mg BID 3 weeks on/1 week off).

B1271002: PF-05212384 in Combination with Irinotecan

Dose Limiting Toxicities

As of the data cutoff date of 30 April 2015, DLTs were experienced by 2 patients following administration of PF-05212384 130 mg QW + irinotecan 180 mg/m2 Q2W. The toxicities included Grade 4 hypokalemia, sepsis, and febrile neutropenia (1 patient), and Grade 3 fatigue (1 patient). Although not strictly meeting the criteria for DLT, 3 patients enrolled at the MTD (PF-05212384 110 mg QW + irinotecan180 mg/m2 Q2W) experienced AEs that were reported by the investigator as DLTs on the case report form. One patient experienced Grade 2 neutropenia, one patient experienced Grade 1 papular rash, and 1 patient experienced Grade 1 constipation and Grade 2 vomiting.

Treatment-Emergent All-Causality Adverse Events

For patients treated with PF-05212384 in combination with irinotecan (Arm C), the most frequent (≥20%) treatment emergent all-causality AEs were nausea (61.4%), diarrhea (52.3%), vomiting (45.5%), decreased appetite (40.9%), fatigue (34.1%), abdominal pain (31.8%), asthenia (27.3%), alopecia (22.7%), and anemia, constipation, mucosal inflammation, pyrexia and rash (20.5% each).

Discontinuations Due to Adverse Events

As of the data cutoff date of 30 April 2015, no patients have discontinued the B1271002 study due to treatment-related AEs following administration of PF-05212384 in combination with irinotecan.

Serious Adverse Events

All patients who experienced SAEs were treated with PF-05212384 130 or 110 mg QW in combination with irinotecan 180 mg/m2 Q2W, a dose which is at or above the MTD of PF-05212384 (110 mg) when given in combination with irinotecan 180 mg/m2 Q2W.

Deaths

As of 30 April 2015, 3 deaths were reported in study B1271002 following administration of PF-05212384 in combination with irinotecan. The events were cerebrovascular accident, lung infection, asthenia, urinary tract infection and convulsion, all unrelated to study drug.

Laboratory Abnormalities

Following administration of PF-05212384 in combination with irinotecan. At the time of the data cutoff, data were available for 44 patients. Most of the hematology test abnormalities were Grades 1 or 2. Grade 3 hematology test abnormalities included white blood cells in 6/44 (13.6%), lymphopenia and anemia in 4/44 (9.1%) each, and absolute neutrophil in 3/44 (6.8%). Grade 4 hematology test abnormalities included neutrophils (absolute) reported in 5/44 patients (11.4%) and lymphopenia reported in 2/44 patients (4.5%) and white blood cells decreased reported in 1/44 (2.3%) patients each. Most of the chemistry test abnormalities were Grades 1 or 2. Grade 3 chemistry test abnormalities included bilirubin(total) in 2/44 (4.5%) patients, hypoalbuminemia in 2/43 (4.3%) patients, AST and ALT in 1/44 (2.3%) patient each, alkaline phosphatase in 3/44 (6.8%) patients, hypermagnesemia in 1/44 (2.3%) patients, hypocalcemia in 2/44 (4.5%) patients, hypokalemia in 3/44 (6.8%) patients, hypomagnesemia in 1/44 (2.3%) patients, hyponatremia in 2/44 (4.5%) patients, hyperglycemia in 3/44 (6.8%) patients, and hypophosphatemia in 2/44 (4.5%) patients. Grade 4 chemistry test abnormalities included hypokalemia reported in 1/44 (2.3%) of patients.

B1271002: PF-05212384 in Combination with PD-0325901

Discontinuations Due to Adverse Events

As of the data cutoff date of 30 April 2015, one patient has discontinued due to AEs (mucosal inflammation) following administration of PF-05212384 in combination with PD-0325901. There were no treatment-related SAEs observed in study B1271002 when treated with PF-05212384 in combination with PD-0325901 as of the data cutoff date of 30 April 2015.

Deaths

As of the data cutoff date of 30 April 2015, 5 deaths had been reported following administration of PF-05212384 in combination with PD-0325901. The events were disease progression, non-small cell lung cancer, cardiac tamponade, hypercalcemia abdominal pain, and pancreatic carcinoma, all unrelated to study drug.

Laboratory Abnormalities

Most of the hematology test abnormalities were Grades 1 or 2. Grade 3 hematology test abnormalities included lymphopenia and anemia in 2/36 (5.6%) patients each, and hemoglobin increased, platelets and neutrophils (absolute) in 1/36 (2.8%) patients each. Grade 4 hematology test abnormalities included white blood cells and lymphopenia reported in 1/36 (2.8%) patients each. Most of the chemistry test abnormalities were Grades 1 or 2. Grade 3 chemistry test abnormalities included hyponatremia in 4/36 (11.1%) patients, hypokalemia in 2/36 (5.6%) patients and AST, ALT, alkaline phosphate, hypophosphatemia, hyperglycemia and hypermagnesemia in 1/33 (3.0%) patient each. Grade 4 chemistry test abnormalities included creatinine, hyponatremia, hypocalcemia and hypoglycemia reported in 1/36 (2.8%) patient each.

Phase 1b Study B2151002 of PF-05212384 in Combination with Docetaxel, Cisplatin, or Dacomitinib in Patients with Advanced Solid Tumors

B2151002 is an ongoing Phase 1b, open-label, double-arm, multicenter, dose-escalation, study of PF-05212384 in combination with docetaxel (Arm A), cisplatin (Arm B) or dacomitinib (Arm C) in patients with advanced solid tumors. The primary objective of the study is to assess safety and tolerability and define the MTD of PF-05212384 in each of the combination arms. Arms A and B

of the study are being conducted in parallel arms of sequential dose levels using a classical 3+3 study design. The data reflects patients treated with PF-05212384 doses of 90 110 mg IV QW in combination with docetaxel 75 mg/m2 IV every 3 weeks (Q3W) in Arm A and doses of 90 and 130 mg QW in combination with cisplatin 75 mg/m2 IV Q3W in Arm B. Arm C is being conducted with a zone design, which consists of a modified 3+3 design that allows opening more than one dose level at the same time. In Arm C, patients have received PF-05212384 doses of 90 and 110 mg IV QW in combination with dacomitinib (30 and 45 mg daily (QD).

Dose Limiting Toxicities

As of the data cutoff date of 30 April 2015, DLTs were experienced by 4 patients following administration of PF-05212384 + dacomitinib. The DLT included the following events; Grade 3 maculopapular rash, Grade 2 fatigue, Grade 3 mucosal inflammation, and Grade 3 pneumonitis (1 patient each). DLT was experienced by 1 patient following administration of PF-05212384 + docetaxel which included Grade 3 mucosal inflammation. There were no DLTs recorded for the PF-05212384+ cisplatin treated patients. At the time of the cutoff date, the MTD had not been established for any of the PF-05212384 combinations tested in B2151002.

Discontinuations Due to Adverse Events

As of the data cutoff date of 30 April 2015, 1 patient had discontinued due to treatment-related AEs pneumonitis following administration of PF-05212384 in combination with dacomitinib. One patient had discontinued due to treatment-related AEs thrombocytopenia following administration of PF-05212384 in combination with docetaxel. No patients had discontinued due to treatment-related AEs following administration of PF-05212384 in combination with cisplatin.

Deaths

As of 30 April 2015, 6 deaths were reported in study B2151002 following administration of PF-05212384 in combination with docetaxel, cisplatin, or dacomitinib, either during treatment, or within 28 days of the last dose of PF-05212384 all due to disease progression.

Phase 2 Study B2151005 of PF-05212384 in Combination with Irinotecan in Patients with Previously Treated Metastatic Colorectal Cancer

Study B2151005 is an ongoing Phase 2 randomized study in patients with advanced colorectal cancer who have received 2 prior systemic therapies in the metastatic setting. The study is designed to determine whether PF-05212384 in combination with irinotecan has superior progression-free survival (PFS) compared to cetuximab in combination with irinotecan. The study includes a non-randomized LIC conducted at Japanese sites to evaluate the safety of PF-05212384 and irinotecan in Japanese patients.

Demographics

As of the cutoff date of 30 April 2015, for patients assigned to receive treatment with PF-05212384 in combination with irinotecan, a total of 19 patients were enrolled to the trial; 13 were treated with PF-05212384 in combination with irinotecan (6 out of 13 were in Japan LIC), while 6 patients were randomized to the treatment arm containing cetuximab in combination with irinotecan.

Treatment-Emergent All-Causality Adverse Events
For patients treated with PF-05212384 in combination with irinotecan (Arm A), the most frequent (≥20%) treatment emergent all-causality AEs were nausea and stomatitis (69.2% each), diarrhea (61.5%), vomiting and decreased appetite (46.2% each), fatigue and neutropenia (38.5% each), alopecia and rash (30.8% each), and abdominal pain, back pain, dizziness and headache (23.1% each). One patient experienced SAE treated with PF-05212384 110 mg QW in combination with irinotecan 180 mg/m2 Q2W.

Deaths
As of 30 April 2015, no deaths were reported in study B2151005 following administration of PF-05212384 in combination with irinotecan, either during treatment, or within 28 days of the last dose of PF-05212384.

Phase 1b/2 Study B2151007 of PF-05212384 in Combination with Irinotecan/fluorouracil/leucovorin (FOLFIRI) in Patients with Previously Treated Metastatic Colorectal Cancer
Study B2151007 is an ongoing Phase 1b/2 randomized study in patients with advanced colorectal cancer who have received 1 prior systemic therapy in the metastatic setting. The study is designed to determine the recommended RP2D of PF-05212384 in combination with FOLFIRI and also to determine whether PF-05212384 in combination with FOLFIRI has superior PFS compared to bevacizumab in combination with FOLFIRI.

Discontinuations Due to Adverse Events
As of the data cutoff date of 30 April 2015, no patients have discontinued due to treatment related AEs following administration of PF-05212384 in combination with FOLFIRI.

Serious Adverse Events
As of the data cutoff date of 30 April 2015 in patients receiving PF-05212384 in combination with FOLFIRI in the B2151007 trial, there were no treatment-related SAEs observed.

Deaths
As of 30 April 2015, no deaths were reported in study B2151007 following administration of PF-05212384 in combination with FOLFIRI, either during treatment, or within 28 days of the last dose of PF-05212384.

1.4.5.3 Investigator Initiated Research (IIR) Studies

Three (3) Investigator initiated research (IIR) studies (WI179493, WI174764, and WI179849) are being conducted with PF-05212384. Due to the limited clinical data available regarding the IIR studies as of the data cutoff date of 30 April 2015, detailed information regarding these studies will be provided as part of the next IB update and incorporated as an amendment to the protocol.

Phase 1b/2 Study WI179493 of PF-05212384 in Combination with Temozolomide in Patients with Recurrent Glioblastoma Multiforme Showing PI3K Pathway Activation
This is a Phase 1b/2 study of the PI3K/mTOR Inhibitor PF-05212384 combined with temozolomide (TMZ) in patients with recurrent glioblastoma multiforme (GBM) showing PI3K

pathway activation. In this study, PF-05212384 is combined with TMZ administered at the fixed dose of 75 mg/m2/day for 22 days of a 28-day cycle. PF-05212384 is dosed IV on a once weekly schedule beginning Cycle 1, Day 1. Patients who have recurrent GBM that has evidence of activation of the PI3K signaling pathway; specifically, either PTEN inactivation or PIK3CA or PIK3R1 mutations are enrolled. The study will be conducted in two sequential parts: dose escalation and dose expansion. Dose escalation will utilize ascending dose levels of PF-05212384 (90 mg, 120 mg and 150 mg) and a standard 3+3 Phase 1 design. Dose expansion will enroll additional patients at either the 150 mg once weekly (the single-agent MTD) dose or one of the lower dose levels if 150 mg once weekly is not well tolerated when combined with TMZ. In each of the 2 parts of the study, patients will be enrolled on 1 of 2 treatment arms, depending on whether surgical resection of the recurrent tumor is planned. As of 30 April 2015, no patients had been enrolled in this study.

Study WI174764: Dose finding Study of PF-05212384 with Paclitaxel and Carboplatin Dose Finding Part

The primary objective of the dose finding part is to determine the MTD and the recommended Phase 2 dose (RP2D) of PF-05212384 in combination with paclitaxel and carboplatin in patients with advanced solid tumors. The trial of this protocol will replicate this data, in part, to verify safety and potential activity of this regimen in NSCLC.

Expansion Phase

The primary objective of the expansion phase is to define the safety and tolerability, also after repeated administrations, of PF-05212384 in combination with paclitaxel and carboplatin. As of 30 April 2015, 4 patients were enrolled in this study.

Serious Adverse Events and Deaths

As of 30 April 2015, no SAEs or deaths were reported in patients treated with PF-05212384 in combination with paclitaxel and carboplatin in this study.

Phase 2 Study WI179849 Evaluating the Efficacy of PF-05212384 for Patients with Myeloid Neoplasm Secondary to Chemo-Radiotherapy (T-AML/MDS) or De Novo Relapsed or Refractory AML

This is a Phase 2 clinical trial evaluating the efficacy of the dual inhibition of PI3K/Akt/mTOR signaling pathway by PF-05212384 for patients with myeloid neoplasm secondary to chemo-radiotherapy (t-AML/MDS) or de novo relapsed or refractory AML. This study is being conducted to evaluate the efficacy of PF-05212384 on the global response after a 4-month treatment calculated by the proportion of complete responses, complete responses with incomplete recovery and partial responses according to the IWG AML and MDS criteria. The treatment is administered in cycles of 28 days for a period of four months or until progression. As of 30 April 2015, no patients were enrolled in this study.

1.4.6 **QTc Prolongation**

Phase 1 (First-in-Human) Study B2151001 of Single Agent PF-05212384 in Patients with Advanced Solid Tumors

At the MTD (154 mg), PF-05212384 was associated with a normal QTcF (ie, <450 msec) in the majority of patients (33/42 patients [78.6%]), with Grade 1 QTcF prolongation in 8 of 42 (19.0%) patients and Grade 3 QTcF prolongation in 1 of 42 (2.4%) patients. At doses above the MTD (19 patients) there was one Grade 1 QTcF prolongation (450 msec to <480 msec [PF-05212384 266 mg]), one Grade 2 QTcF prolongation (480 msec to <500 msec [PF-05212384 222 mg]), and no Grade 3 toxicity. Based on the low incidence of QTcF prolongation overall and, more specifically, at doses above the MTD, which suggest a lack of dose effect relationship between PF-05212384 dose and QTcF, PF-05212384 is not likely associated with QTc interval prolongation. One patient (10020216, a 56-year-old female at the PF-05212384 154 mg dose level) had a maximum QTcF interval of ≥500 msec. However, based on patient's concomitant medical condition that included hypertension, probable myocardial ischemia, and electrolyte imbalance, and the likely low serum concentration of the study compound (due to the elapsed time between the last PF-05212384 administration and the appearance of the event), it is considered unlikely that the reported QTcF prolongation was related to the study drug.

Phase 2 Study B1271004 of Single Agent PF-05212384 in Patients with Advanced Endometrial Cancer

Table 6.2-45 shows QTcF changes from Phase 2 Study B1271004 with single agent PF-05212384 following administration of 154 mg QW PF-05212384. In study B1271004, at the MTD for PF-05212384 (154 mg) the mean QTcF interval change was 24.9 ± 28.19 msec. Although there was greater variation as observed with the greater standard deviation, the mean change in QTcF interval in this study was smaller than the mean change observed in Phase 1 FIP study B2151001 (28.6 ± 15.25 msec). PF-05212384 was associated with a normal QTcF (ie, <450 msec) in 31/39 (79.5%) patients. Grade 1 QTcF prolongation was documented in 6/39 (15.4%) patients and Grade 2 prolongation was observed in 2/39 (5.1%) patients. There were no patients with QTcF ≥500 msec.

Phase 1b Study B1271002 with PF-05212384 in Combination with Irinotecan and PF-05212384 in Combination with PD-0325901 in Patients with Advanced Solid Tumors

In study B1271002, the mean QTcF interval change was 25.6 ± 15.31 msec when PF-05212384 was combined with irinotecan and was 19.5 ± 11.14 msec when PF-05212384 was combined with PD-0325901; these values were similar to the mean change observed in Phase 1 FIP Study B2151001 (28.6 ± 15.25 msec). PF-05212384 in combination with irinotecan was associated with a normal QTcF (ie, <450 msec) in 35/44 (79.5%) patients. Grade 1 QTcF prolongation was documented in 7/44 (15.9%) patients and Grade 2 prolongation was observed in 1/44 (2.3%) patients. There was 1 patient with QTcF ≥500 msec which was not considered medically significant. PF-05212384 in combination with PD-0325901 was associated with a normal QTcF (ie, <450 msec) in 31/36 (86.1%) patients and Grade 1 QTcF prolongation in 5/36 (13.9 %) patients. There were no patients with > Grade 1 prolongation.

Phase 1b Study B2151002 with PF-05212384 in Combination with docetaxel, cisplatin, or dacomitinib in Patients with Advanced Solid Tumors

In study B1271002, the mean QTcF interval change was 25.6 ± 15.31msec when PF-05212384 was combined with irinotecan and was 19.5 ±1 1.14 msec when PF-05212384 was combined with PD-0325901; these values were similar to the mean change observed in Phase 1 FIP Study B2151001 (28.6 + 15.25 msec).

PF-05212384 in combination with cisplatin was associated with a normal QTcF (ie, <450 msec) in all of the patients treated to-date in the trial. PF-05212384 in combination with dacomitinib was associated with a normal QTcF (ie, <450 msec) in 26/27 (96.3%) patients treated to-date in the trial. PF-05212384 in combination with docetaxel was associated with a normal QTcF (ie, <450 msec) in 17/19 (89.5%) patients treated to-date in the trial. Grade 1 QTcF prolongation was observed in 2/27 (7.4%) patients who were treated with PF-05212384+dacomitinib and in 2/19 (10.5%) patients who were treated with PF-05212384+docetaxel. There were no patients with > Grade 2 prolongation. Although there were no cases of QT prolongation in the ECGs collected in the study, there was a patient in whom an unscheduled ECG was performed which was documented as demonstrating Grade 3 QT prolongation. The patient, (10091001) was a 64-year-old man with primary diagnosis of HNSCC who had a history of atrial fibrillation who was enrolled in Arm C (PF-05212384 in combination with dacomitinib). Grade 3 QTcF prolongation was identified 5 days following last dose of PF-05212384. At the time of the event, he was also experiencing Grade 2 hypoxia and Grade 2 mucositis and mild hypokalemia and hypomagnesemia for which he received K-dur and magnesium sulphate replacement therapy. The investigator considered the QT prolongation as unrelated to both PF-05212384 and dacomitinib.

Phase 2 Study B2151005 of PF-05212384 in Combination with Irinotecan in Patients with Metastatic Colorectal Cancer

In the phase 2 study B2151005, the mean QTcF interval change was 15.7 ± 8.09 msec; these values were lower than the mean change observed in Phase 1 FIP Study B2151001 (28.6 ± 15.25 msec). PF-05212384 in combination with irinotecan was associated with a normal QTcF (ie, <450 msec) in all 11/12 (91.7%) patients treated to-date in the trial. Grade 1 QTcF prolongation was observed in 1/12 (8.3%) patients. There were no patients with > Grade 2 prolongation.

Phase 2 Study B2151007 of PF-05212384 in Combination with FOLFIRI Chemotherapy

In the phase 2 study, B2151007, the mean QTcF interval change was 34.5 ± 8.09 msec; these values were lower than the mean change observed in Phase 1 FIP Study B2151001 (28.6 ± 15.25 msec). PF-05212384 in combination with FOLFIRI was associated with a normal QTcF (ie, <450 msec) in 14 /16 (87.5%) patients treated to-date in the trial. Grade 1 QTcF prolongation was observed in 2/16 (12.5%) patients. There were no patients with > Grade 2 prolongation.

1.4.7 **Efficacy**

Preliminary efficacy data is only available in the single agent trials B2151001 and B1271004.

Phase 1 (First-in-Human) Study B2151001 with Single Agent PF-05212384 in Patients with Advanced Solid Tumors

The objective response rate (ORR) of single agent PF-05212384 in 77 response evaluable patients with advanced solid tumors was 2.6% (partial response [PR]); overall, 13% of patients were determined to have achieved a clinical benefit response (CBR).

Phase 2 Study B1271004 with Single Agent PF-05212384 in Patients with Advanced Endometrial Cancer

As of 30 April 2015, of the 38 patients treated with PF-05212384 for whom there was tumor assessment data at baseline and post-baseline, 1 (2.6%) patient had a CR, 5 (13.2%) patients had a PR and 9 (23.7%) patients had stable disease (SD) for at least 16 weeks. Overall, 39.5% of patients were determined to have achieved a CBR.

Phase 1b Study B1271002 of PF-05212384 in Combination with Irinotecan and PF-05212384 in Combination with PD-0325901 in Patients with Advanced Solid Tumors

As of 30 April 2015, of the 44 patients treated with PF-05212384 in combination with irinotecan, no patient had a CR, 1 (2.3%) patient had a PR and 22 (50.0%) patients had SD or no response and objective progression was observed in 18 (41.1%) patients. ORR was not observed in 1 (2.3%) patients. As of 30 April 2015, of the 36 patients treated with PF-05212384 in combination with PD-0325901, no patient had a CR, 3 (8.3%) patients had a PR, 7 (19.4%) patients had SD or no response and 17 (47.2%) patients had objective progression. An objective response was observed in 3 (8.3%) patients.

Phase 1b Study B2151002 of PF-05212384 in Combination with Docetaxel, Cisplatin, or Dacomitinib in Patients with Advanced Solid Tumors

As of 30 April 2015, of the 19 patients treated with PF-05212384 in combination with docetaxel, no patient had a CR, 1 (5.3%) patient had a PR, 8 (42.1%) patients had SD or no response and 6 (31.6%) patients had objective progression. An objective response was observed in 1 (5.3%) patient. As of 30 April 2015, of the 16 patients treated with PF-05212384 in combination with cisplatin, no patient had a CR, 4 (25.0%) patients had a PR, 6 (37.5%) patients had SD or no response and 2 (12.5%) patients had objective progression. An objective response was observed in 4 (25.0%) patients. As of 30 April 2015, of the 28 patients treated with PF-05212384 in combination with dacomitinib, 1 (3.6%) patient had a CR, 3 (10.7%) patients had a PR, 14 (50.0%) patients had SD or no response and 6 (21.4%) patients had objective progression. An objective response was observed in 4 (14.3%) patients.

Phase 2 Study B2151005 of PF-05212384 in Combination with Irinotecan in Patients with Previously Treated Metastatic Colorectal Cancer

As of 30 April 2015, of the 7 patients treated with PF-05212384 in combination with irinotecan, no patient had a CR, 1 (14.3%) patient had a PR, 3 (42.9%) patients had SD or no response and 3 (42.9%) patients had objective progression. An objective response was observed in 1 (14.3%) patient. As of 30 April 2015, of the 6 patients in LIC treated with PF-05212384 in combination

with irinotecan, no patient had a CR and PR, 4 (66.7%) patients had SD or no response and 2 (33.3%) patients had objective progression. An objective response was not observed in any of the patients.

Phase 1b/2 Study B2151007 of PF-05212384 in Combination with FOLFIRI in Patients with Previously Treated Metastatic Colorectal Cancer

As of 30 April 2015, of the 17 patients treated with PF-05212384 in combination with FOLFIRI, no patient had a CR, 1 (5.9%) patient had a PR, 5 (29.4%) patients had SD or no response and 6 (35.3%) patients had objective progression. An objective response was observed in 1 (5.9%) patient.

1.5 CARBOPLATIN (CBDCA) (NSC-241240)

1.5.1 Description

Carboplatin (CBDCA) is a hydrophilic platinum coordination compound and is an analog of cisplatin, producing intrastrand DNA cross-links.

1.5.2 Toxicology

Human Toxicology: Side effects of carboplatin (CBDCA) include myelosuppression, nausea, vomiting, abdominal pain, diarrhea and constipation. Other toxicities include allergic reaction (including hypersensitivity, i.e., rash, urticaria, erythema, pruritus, bronchospasm and hypotension), peripheral neuropathy, paresthesias, loss of hair, hearing loss, visual disturbances and change in taste. Serum creatinine elevations and blood urea elevations have occurred as well as abnormal liver function tests and decreased serum electrolyte values. Although rare, pain, asthenia, cardiovascular, respiratory, genitourinary and mucosal side effects have occurred in some patients. Cancer-associated hemolytic uremic syndrome has been reported rarely. The renal effects of nephrotoxic compounds may be potentiated by carboplatin. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds or mannitol. This drug should not be used in patients with severe bone marrow depression or significant bleeding. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Pregnancy and Lactation: Carboplatin may cause fetal harm; therefore women of childbearing potential should be advised to avoid becoming pregnant.

1.5.3 Pharmacology

Kinetics: The differences in potencies of carboplatin and cisplatin are due to differences in aquation rates. The initial half-life is 1.1 - 2.0 hours and the post-distributional half-life is 2.6 - 5.9 hours. Sixty-five percent of the dose is excreted in the urine within twelve hours. Carboplatin is not bound to plasma proteins.

Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous injection. Each vial contains equal parts by weight of carboplatin and mannitol. Immediately before use, the

content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water, or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/mL. Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride Injection, USP (NS).

Storage and Stability: Unopened vials of carboplatin for injection are stable for the life indicated on the package when stored at controlled room temperature 15° - 30°C, and protected from light. When reconstituted as directed, the solution of carboplatin exhibits no decomposition for 8 hours at room temperature (25°C). Like cisplatin, this drug should not be given through aluminum needles.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded eight hours after dilution.

Administration: Intravenous.
Supplier: Carboplatin is commercially available for purchase by the third party.
Please refer to the Physician Desk Reference and package insert for complete Information.

1.6 **PACLITAXEL, Taxol® (NSC-673089)**

1.6.1 **Description**

Chemistry: Paclitaxel is a diterpene plant product found in the needles and bark of the western yew, *Taxus brevifolia*. The marketed formulation is prepared in a semi-synthetic process.
Molecular Weight: 853.9
Empirical Formula: $C_{47}H_{51}NO_{14}$
Description: Clear viscous fluid

1.6.2 **Toxicology**

Human Toxicity:
Dose-limiting toxicity is myelosuppression with reversible granulocytopenia, anemia, and thrombocytopenia. Allergic reactions occur in up to 8% of patients receiving paclitaxel as an intravenous infusion over 6 to 24 hours. These can be acute anaphylactoid reactions to include flushing, hypotension, and bronchospasm; dermatitis and pruritus are also observed. Hypertension has also been seen, and may be related to concomitant medication with dexamethasone. Premedication with diphenhydramine, cimetidine, and dexamethasone appears to diminish the incidence of these reactions. Neurotoxicity can include distal painful paresthesias. Rarely, this toxicity has required discontinuation of drug due to pain, impairment of fine motor skills, or

difficulty ambulating. Experience to date suggests that this neuropathy is reversible. Rarely, associated forms of neurotoxicity have included taste perversion, seizures, and mood changes. Some patients have reported vision abnormalities such as blurred vision, "flashing lights" and scintillating scotomata. Ischemic or infarcted colon, sometimes with involvement of other parts of the gastrointestinal tract, has also been seen. Patients reporting abdominal discomfort should be monitored closely. These events generally occurred while the patients were severely neutropenic. They may be most consistent with neutropenic enterocolitis (typhlitis). Although increased SGOT, SGPT, bilirubin and alkaline phosphatase, as well as hepatic failure and hepatic necrosis have been seen, one patient receiving this drug has also experienced hepatic encephalopathy, and two incidences of pancreatitis have been noted. Neuroencephalopathy has also been reported. Pulmonary toxicities that have occurred are pneumonitis and radiation pneumonitis (following concomitant paclitaxel and radiation). Other non-hematologic reactions include: diarrhea, alopecia, myalgias and arthralgias, nausea or vomiting, mucositis (stomatitis and pharyngitis), lightheadedness, myopathy and fatigue. Less commonly, cardiotoxicity has been associated with paclitaxel administration, to include arrhythmias (sinus bradycardia, ventricular tachycardia, atrial arrhythmia, and heart block), and myocardial infarction. Skin reactions including erythema, induration, tenderness, ulceration, radiation recall, rash and nail changes have occurred including discoloration of fingernails and separation from nail bed.

Pregnancy and Lactation: Paclitaxel may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats. In these studies, paclitaxel was shown to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorption and embryo-fetal deaths. No information is available on the excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

1.6.3 **Pharmacology**

Formulation: Sterile solution containing 6 mg/ml in a 5 ml vial (30 mg per vial) in polyoxyethylated castor oil (Cremaphor EL) 50% and dehydrated alcohol, USP, 50%. There are also vial sizes of 100 mg and 300 mg.

Solution Preparation: Paclitaxel is reconstituted by diluting the total dose in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (D5W) to maintain a paclitaxel concentration between 0.3 and 1.2 mg/ml. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremaphor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtrations should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II or IVEX-HP or equivalent) into the IV fluid pathway distal to

the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Administration of Paclitaxel: Paclitaxel, at the appropriate dose, will be given as an intravenous infusion as specified in the protocol, diluted in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) which are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered.

Storage and stability: The intact vials of paclitaxel should be stored between 2-25°C. Based on stability data for Taxol® made from either natural or semisynthetic paclitaxel, stored for up to 12 months at 40°C, potency losses were within the range of 2.0 to 2.4 percent per year. Samples stored for up to 3 months at 60°C lost potency at rates corresponding to 20 to 40% per year. Accordingly, vials left out in a warm place for a few days should still be satisfactory for use. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours. Vials will be labeled with a firm expiration date.

Supplier: Paclitaxel is commercially available for purchase by the third party.
Please refer to the Physician Desk Reference and package insert for complete information.

2. STUDY POPULATION

2.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

A. Signed IRB-approved informed consent prior to any study-related procedures
B. Age of 18 years or older
C. Advanced-stage unresectable NSCLC, as confirmed by pathological and/or radiological analysis (subjects will be classified as having advanced disease if they were not eligible for, or had disease progression after, surgical or locoregional therapies)
D. Prior chemotherapy will be allowed for other invasive malignancies, provided therapy was completed at least five years before the start of protocol therapy, and participants have recovered from all toxicities of that prior therapy
E. Participants may have received prior chemotherapy for NSCLC; in the Phase I portion, subjects who have previously received paclitaxel and/or carboplatin will be allowed. In the phase II portion, subject must not have received prior carboplatin or a taxane within the prior five years.
F. In the Phase II portion, subjects must have disease which lacks PTEN expression by immunohistochemistry, or has known prior activating PI3K or inactivating PTEN gene mutations (mutations will not be assayed for specifically)
G. Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2
H. Life expectancy ≥ 12 week
I. Participants must have measureable disease by RECIST criteria

J. Absolute neutrophil count ≥ 1500 mm^3 (individuals with benign ethnic neutropenia may be enrolled if they have no evidence of infectious diathesis, or febrile neutropenia at the time of enrollment)
K. Platelet count ≥ 100×10^9 L
L. Hgb ≥ 8.5 g/dL (subjects may receive transfusions to achieve this, in the absence of overt bleeding)
M. Total Bilirubin ≤ 2 mg/dL
N. AST/ALT ≤ 3 times the upper limit of normal range
O. Serum creatinine ≤1.5 times the upper limit of the normal range
P. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for at least 6 months after the last dose of study drug to minimize the risk of pregnancy. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

   WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:
   - Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or
   - For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.

Q. Males with female partners of child-bearing potential must agree to use physician-approved contraceptive methods (*e.g.*, abstinence, condoms, vasectomy) throughout the study and should avoid conceiving children for 6 months following the last dose of study drug.

2.2 **Exclusion Criteria**

Subjects with any of the following will not be eligible for study participation:

A. Uncontrolled cardiac disease, congestive heart failure, angina, arrhythmias or hypertension.
B. Myocardial infarction or unstable angina within 2 months of treatment.
C. Subjects who are carboplatin- or paclitaxel-resistant.
D. Known human immunodeficiency virus (HIV) infection or chronic active Hepatitis B (subjects will not be screened for this).
E. Active clinically serious infection > CTCAE Grade 2.
F. Thrombotic or embolic events such as a cerebrovascular accident including transient ischemic attacks within the past 6 months.
G. Pulmonary hemorrhage/bleeding event ≥ CTCAE Grade 2 within 4 weeks of first dose of study drug.
H. Any other hemorrhage/bleeding event ≥ CTCAE Grade 3 within 4 weeks of first dose of study drug.
I. Serious non-healing wound, ulcer, or bone fracture.
J. Evidence or history of bleeding diathesis or coagulopathy

K. Major surgery, open biopsy or significant traumatic injury within 4 weeks of first study drug
L. Women or men of childbearing potential who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 6 months after the last dose of study drug
M. Women who are pregnant or breastfeeding.
N. History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician.
O. Prisoners or subjects who are involuntarily incarcerated.
P. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.
Q. Subjects demonstrating an inability to comply with the study and/or follow-up procedures.

2.3 **Inclusion of Women and Minorities**

Both men and women and members of all races and ethnic groups are eligible for this trial.

3. REGISTRATION PROCEDURES

All subjects must be registered with the UF Health Cancer Center prior to participation in this trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the designated Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

4. STUDY TREATMENT

All subjects entering the screening phase will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number.

4.1 **Treatment Schedule/Administration**

This study is an open-label, non-randomized, sequentially-enrolling phase Ib-II trial in subjects with NSCLC who would be eligible for paclitaxel and carboplatin.

4.2 **Overall Treatment Plan**

This is a non-randomized, Phase Ib-II trial to assess clinical safety and potential benefit of PF-05212384 when administered to subjects with NSCLC who are receiving a baseline regimen of paclitaxel and carboplatin. All treatment will be administered on an outpatient basis. Before the 1st dose of treatment, subjects will undergo clinical, pathological and radiographic tumor assessment. PF-05212384 will be administered IV on days 2, 9, 16 of the 21-day treatment cycle.

The phase Ib portion will study dose escalations in separate cohorts using the dose levels of PF-05212384 listed in the table below. The phase II portion will consist of a two stage Simon design. The doses for paclitaxel (200 mg/m^2, Q21 days) and carboplatin (AUC=6, Q21 days) do not adjust as part of the study design.

Dose Cohort	PF-05212384 Dose (mg, days 2, 9, 16)
1	110
2	150
3	180

During the first stage, cohorts of 3 participants each will be sequentially enrolled to each increasing dose level, beginning with dose level 1 (110 mg) until the first dose limiting toxicity occurs, or safely accrued to dose level 3. The level determined to be the maximal tolerable dose will have three additional subjects to better define tolerability prior to initiating the phase II portion. Once that happens, the first stage (phase Ib) will end and the trial will move to the second stage (phase II). During the second stage, initially 10 subjects will be enrolled; in the absence of grade 3-5 toxicity, if at least one response has been observed, then accrual will continue to 29 subjects. The MTD of PF-05212384 in combination with a platinum-based regimen appears to exceed 215 mg, and at this time there will be no attempt to exceed that dose level.

Dose reduction or interruption of PF-05212384 for toxicity may take place at any time during the study. Toxicity grading is based on NCI-CTCAE, v 4.0.3. Dose level reductions are to the immediately preceding dose cohort. If subjects do not tolerate the second dose reduction, PF-05212384 is to be discontinued.

Eligible subjects will include those with radiographically-staged locally advanced or metastatic NSCLC. For the phase I portion, subjects may have previously received paclitaxel and/or carboplatin. For the phase II portion, subjects must not have received prior carboplatin or a taxane within the prior five years to study enrollment. Subjects who receive radiation therapy to any indicator lesion must have demonstrated progressive growth of the lesion to be assessable; be willing to use contraception and if females or child-bearing capacity, are neither pregnant nor lactating; are greater than 18 years old and have an anticipated life expectancy of at least 12 weeks; have normal end-organ function and limited comorbidities, and are able to provide written informed consent.

The initial dose of paclitaxel is 200 mg/m^2. The initial dose of carboplatin is AUC=6 by modified Calvert formula (see below). Carboplatin is given after paclitaxel infusion is completed. Both drugs with be given sequentially on Day 1 of the 21-day treatment cycle (± 3 days, to allow for weekends, holidays, unforeseen events not related to toxicity). Serum creatinine must be repeated and creatinine clearance calculated within 3 days prior to each carboplatin dose. In subjects whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing.

Paclitaxel	200 mg/m^2	3 hour IV infusion	Day 1 of each 21 day cycle x 6 cycles
Carboplatin	AUC = 6	30 minute IV infusion immediately following paclitaxel	Day 1 of each 21 day cycle x 6 cycles
PF-05212384	110 mg 150mg 180mg	30 minute IV infusion	Days 2, 9, 16 of each 21 day cycle x 6 cycles

Guidelines for Carboplatin Administration
The carboplatin dose (mg) = AUC x (CrCl + 25) where AUC = 6 depending on the dose level. The creatinine clearance will be calculated using a serum creatinine obtained within 3 days prior to each dose. Carboplatin dose will be based on GFR* (glomerular filtration rate) based on the measurement of creatinine clearance where GFR is calculated using the Cockroft-Gault Formula:
CrCI = [(140 - age) x actual body weight (kg)**] / [72 x serum creatinine***]
Multiply this number by 0.85 if the subject is female.

* GFR = calculated creatinine clearance determined using the Cockroft-Gault Formula based on age, weight (actual body weight) and serum creatinine.
** Use current (actual) weight. This should be actual weight but not exceed 140% of IBW.
*** In subjects whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing.

Please note that: GFR should not exceed 125 m/min. Hence, the maximum total carboplatin dose should NOT exceed 900 mg.

All subjects should be pre-medicated with:

Agent	Dose	Route	Duration
Dexamethasone	20 mg	PO/IV	12 and 6 hours prior to paclitaxel*
Diphenhydramine	50 mg	IV	30 minutes prior to paclitaxel
plus one of the following:			
Ranitidine	50 mg	IV	30 minutes prior to paclitaxel
Cimetidine	300 mg	IV	30 minutes prior to paclitaxel
or			
Famotidine	20 mg	PO/IV	30 minutes prior to paclitaxel

* Alternatively, a single intravenous dose of 20 mg may be given 30 minutes

prior to paclitaxel injection.

CAUTION: Allergic reactions may occur during or following chemotherapy administration. As a routine precaution, subjects enrolled in this study will be observed closely for any potential adverse events by the medical staff from the start of the chemotherapy infusion to one hour after the end of the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. Vital signs (blood pressure, heart rate, respiratory rate and temperature) should be checked prior to the administration, midway through the infusion, at the completion of the infusion and 1 hour post the infusion. Should an allergic or infusion reaction to chemotherapy occur, the subject must be treated according to the best available medical practice. The subject's blood pressure and heart rate should be monitored during the chemotherapy infusion. (Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended.) Epinephrine and diphenhydramine for injection should be readily available during the infusion, for emergency treatment of hypersensitivity reactions.

4.3 Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

During the first stage, cohorts of 3 participants each will be sequentially enrolled to each increasing dose level, beginning with dose level 2 (150 mg) until the first dose limiting toxicity occurs. Once that happens, the first stage will end and the trial will move to the second stage. During the second stage, subjects will be enrolled in cohorts of one using the Bayesian CRM design with a targeted dose limiting toxicity rate of 25%. The design assumes an empiric model and a total sample size from both stages of 41 subjects.

Definition of MTD:
The maximum tolerated dose of PF-05212384, in combination with paclitaxel and carboplatin, will be determined by the dose escalation rules summarized in Section 4.2 and 9.2.

Definition of DLT:
DLT will have occurred when the subject has one or more Grade 4 hematologic or nonhematologic toxicities. Exceptions will be made for alopecia and non-febrile neutropenia, which are nearly universal with the use of any taxanes. Grade 3 or greater neuropathy will also be considered as a dose limiting toxicity. By convention, a DLT must occur in the first cycle of the combination and must be at least possibly attributed to the treatment regimen. Toxicities occurring in later cycles will not be considered as a DLT, though they may represent cumulative toxicities of the regimen and thus may limit the number of cycles which may be delivered; example of this are neuropathy related to cisplatin, oxaliplatin, or taxanes administration, or cardiomyopathy due to anthracycline or anthracenedione administration. Toxicities will be graded according to the NCI CTCAE Version 4.0.3.

4.4 Chemotherapy Guidelines

Subjects are to receive PF-05212384 at an initial dose of 110 mg on days 2, 9, and 16 of every 21-day cycle, with paclitaxel and carboplatin as above, with adequate pre-medications and anti-emetics, though the specific agents will be at the discretion of the treating oncologist, within

accepted FDA, American Society of Clinical Oncology, and National Comprehensive Cancer Network guidelines.

In the absence of obvious rapid disease progression, subjects will receive two cycles of protocol therapy (six weeks) before an objective response determination is made by computed tomography or magnetic resonance imaging. Subjects will be reassessed radiographically every other cycle. Subjects will continue to receive protocol therapy until disease progression unless a complete remission is obtained, in which case subjects will receive at least two additional cycles of protocol therapy, and then may hold further active therapy at the discretion of the treating physician. Subjects will receive a maximum of six cycles of protocol therapy; after completion of six cycles, subjects may receive maintenance therapy with erlotinib, pemetrexed, or bevacizumab, as indicated.

In the absence of a decline in performance status or comorbid disease, subjects will continue until documentation of disease progression, or intolerable toxicity, or six cycles, whichever occurs first. Subjects who experience a disease progression through protocol therapy will be offered alternative chemotherapy or palliative care, after discussion with his or her treating physician.

Subjects who experience a CR should receive two additional cycles of protocol therapy following the documentation of a CR, however, no subject will receive more than six cycles of protocol therapy. Subjects who experience a CR due to local consolidative therapy should likewise receive two additional cycles of chemotherapy as described in the protocol.

4.5 **Concomitant Therapy**

Relevant medical history should be obtained at screening and include prior medications and treatment history. All medications taken within 1 week prior to screening, regardless of indication, should be recorded. An exception will be for any monoclonal antibodies which are received within the 6 weeks prior to the initiation of therapy.

Any therapy or medication (except study drugs), administered from screening until 28 days after the last dose of either study drug, is considered a concomitant therapy or medication. However, if another course of anti-cancer therapy is initiated prior to the 28-day follow-up period visit; a record of concomitant medications will no longer be performed. If the use of any concomitant treatments (medications or procedures) becomes necessary, the treatment must be recorded, including the name of the drug or treatment, dose, route, date, indication for use, expected duration, and frequency of treatment. Assessment and documentation of concomitant medications will be done at each visit.

4.5.1 **Allowed Concomitant Therapy**

Subjects are to continue their medications for chronic non-malignant diseases that they were receiving prior to study enrollment. Antibiotics are not an exception to enrollment, but must have been completed for at least 7 days prior to initiating study therapy. There may still be potential ill-defined interactions between PF-05212384 and CYP3A4 inhibitors and CYP3A4 promoters.

Although caution and careful monitoring are recommended when use of these compounds is necessary, use of these compounds does not exclude subjects from participating in this trial.

Subjects taking warfarin or other warfarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

4.5.2 **Prohibited Concomitant Therapy**

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than the study drug in this trial
- Radiation therapy

NOTE: Radiation therapy to a symptomatic solitary lesion may be considered on an exceptional case by case basis after consultation with sponsor-investigator. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines, and are not allowed.

4.6 **Dose Modifications**

The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events Version 4 (CTCAE) will be used to grade toxicity (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

4.6.1 **Dose Modification Table**

See below for modifications of paclitaxel and carboplatin, for adverse events which are possibly, probably, or likely due to either drug.

Hematologic Requirements for Day 1 of Each Cycle
Dose delay based on hematologic counts the day of treatment: The ANC count must be ≥1,500/mcl and the platelet count ≥ 100,000/mcl on the day of planned treatment. If this recovery is not achieved by the day of treatment, the next cycle will be delayed until recovery occurs or a maximum of 2 additional weeks have passed (a total of five weeks since the beginning of the prior cycle). If a delay is > 3 weeks based on these parameters, discontinue all three.

Dose Level	Carboplatin (AUC)	Paclitaxel (mg/m^2)
0	6	200
-1	5	175
-2	4	150

If subjects require a dosage reduction of paclitaxel and carboplatin for toxicity, then they will also receive a concomitant reduction of the dose of PF-05212384 by one dosing cohort level. Those who still experience the same level of toxicity after a dosage reduction will receive a dose decrease to the next lowest dosing cohort. If a subject has been dose decreased to the lowest dosing cohort, then the will be taken off of protocol therapy, though they may continue to receive paclitaxel and carboplatin alone, at their attending physician's discretion.

Dose Modification:
Intra-patient dose reduction and dose interruption will be permitted once a subject has experienced drug-related toxicity provided that the criteria for subject withdrawal from study treatment have not been met. All intra-patient dose reductions are relative to the lowest dose of the current cycle.

There will be no intra-patient dose escalation. Dose adjustments are to be made according to the level of toxicity experienced. Toxicity will be graded using NCI CTCAE (version 4.0.3). Treatment may be delayed no more than two weeks to allow recovery from toxicity. All toxicities, unless otherwise specified below, should resolve to grade 1 prior to beginning treatment.

4.6.2 Non- Hematologic Toxicity

Cardiac Toxicity - Carboplatin and Paclitaxel
If a subject develops chest pain or arrhythmia during the infusion, the infusion should be stopped. Manage any arrhythmias according to standard practice. Subjects who experience chest pain during paclitaxel infusion should not restart paclitaxel until a cardiac ischemic event has been ruled out. Subjects will be removed from paclitaxel and carboplatin treatment in cases of symptomatic arrhythmias or AV block (except first degree) or other heart block. In case of first degree AV block, subject may continue paclitaxel infusion with continuous cardiac monitoring during the infusion, at the discretion of the treating physician.

Hypersensitivity Reactions - Paclitaxel
Caution: Subjects who have a mild to moderate hypersensitivity reaction should be re-challenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended. For moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort), stop the infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. After recovery of symptoms, resume infusion at a low rate, 20 mg/hr for 15 minutes. If no further symptoms, resume at full dose rate until infusion is complete. If symptoms recur, the infusion will be stopped. The subject should receive no additional paclitaxel for that cycle, but may be retreated after discussion with the study PI. For severe life threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilator therapy, generalized urticaria), stop the infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present that is not

responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. The subject will be taken off paclitaxel treatment.

Dose Modifications for Non-Hematologic Toxicities:
For Grade 3 and 4 toxicities, treatment should be withheld until the toxicity resolves to Grade 1 or less (or to baseline), then reinstituted (if medically appropriate) at a one level dose reduction. Nausea and vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy. All agents should be dose reduced in cases where either agent may be the cause of a given toxicity. Subjects must meet pre-treatment laboratory criteria (as specified in the inclusion criteria) at Day 1 of each cycle to receive therapy administration. Subjects will not be eligible for further treatment if resolution of toxicities requires a greater than 3-week delay in the start of the next cycle (five weeks from the start of the prior cycle).

4.6.3 **Hematologic Toxicity**

Dose Modifications for Hematologic Toxicity:
Grade 1, 2 and 3 myelosuppression (neutropenia, thrombocytopenia), with recovery to pre-treatment lab criteria as specified in the inclusion criteria, does not require dose modification. Grade 3 or 4 lymphopenia does not require dose reduction. Subjects with a febrile Grade 4 neutropenia >7 days or Grade 4 neutropenia associated with fever (one reading of oral temperature > 38.5° C, or three readings of oral temperature > 38.0° C in a 24-hour period) or Grade 4 thrombocytopenia >7 days should be retreated after recovery at a one-dose level reduction during subsequent cycles. If any of these toxicities recurs, the subject should be dose reduced again in all subsequent cycles after recovery to pre-treatment lab criteria as specified in the inclusion criteria. Subjects will not be eligible for further treatment if resolution of toxicities requires a greater than 2-week delay in the start of the next cycle. Subjects who need two dose level reductions of paclitaxel and carboplatin, or a dose reduction of PF-05212384 to less than Dose Level 1 should discontinue from the study.

4.7 **Supportive Care Guidelines**

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antidiarrheals, analgesics, etc., when appropriate. Bisphosphonates or denosumab are allowed for subjects with bone metastases.

In the Phase II portion of this study, prophylactic oral mucositis therapy may be administered with an oral steroid rinse and spit agent. Refer to Section 4.7.1 for the management of oral mucositis in the Phase I portion of this study.

4.7.1 Special Warnings and Precautions for Use

Oral Toxicity Management

In the Phase I/dose escalation portion of this protocol, a prophylactic steroid oral rinse and spit agent, or any other type of anti-oral mucositis therapy, use should be avoided. Active therapy should be administered at the first prodromal signs of mucositis, i.e.; xerostomia, sensory changes,

or any new oral symptoms reported by a subject. These listed symptoms may precede oral ulceration and stomatodynia.

During the Phase II portion of study, with the MTD is established, prophylactic oral mucositis therapy may be administered. An oral steroid rinse and spit agent should be given to subjects; in this setting, a magic mouthwash (which includes anesthetic agents) is not the best therapy for oral mucositis.

5. TREATMENT DISCONTINUATION

5.1 Removal of Subjects From Study

Subjects who discontinue participation in the clinical study on their own or subjects who are withdrawn by the investigator, for reasons other than completion of treatment, disease progression or toxicity, will be defined as premature withdrawals.

Subjects who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these subjects will be maintained by the study site.

5.2 Criteria For Study Treatment Discontinuation

A subject will be discontinued from protocol therapy under the following circumstances:

- Any adverse event which, in the Investigator's opinion, requires termination of the study medication.
- Disease progression, unless at the discretion of the principal investigator (in collaboration with any co-sponsors or collaborators) continued treatment with study drug is appropriate.
- Substantial non-compliance (>25% of missed doses accounting for delays and dose modifications per protocol or instructions from research team staff for AEs), with the requirements of the study.
- The subject presents with a beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event.
- The subject uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- The development of a second malignancy that requires treatment, which would interfere with this study.
- The subject is lost to follow-up.
- Interruption in study drugs administration for greater than 21 days (see Dose Modification section).
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree.

The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. If a subject is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the subject is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all subjects are followed up for survival status after the Final Visit.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all subjects participating in the study, even for a brief period of time. Subjects who discontinue following entry will have relevant information completed and recorded on the CRF. All subjects who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any subject should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the UF Health Data Integrity and Safety Committee (DISC).

5.3 **Replacement of Subjects**

Subjects will be replaced if they have not received any doses of study drug prior to their continuing participation in the protocol for any reason, or if the subject wishes to discontinue participation in the protocol, but is not discontinued for disease progression, toxicity, or any of the reasons listed in section 5.2.

6. STUDY PROCEDURES

6.1 Study Schedule of Events

Day of Protocol	Baseline[2]	Day 1, Each Cycle	Within one calendar week of Day 1, odd cycles	Day 2, 9, 16, Each Cycle	Off Treatment	Off Study
Studies:						
H&P[1] / PS / VS & TOX	**X**	**X**			**X**	**X**
CBC w/ Diff.	**X**	**X**		**X[4]**	**X**	**X**
CMP	**X**	**X**			**X**	**X**
UA and Pregnancy Test	**X**					
Diagnostic Imaging Scan / TA[3]	**X**		**X**			**X**
ECG	**X**			**X[5]**		
Treatment:						
PF-05212384, IV [6]				**X**		
Paclitaxel 200 mg/m^2		**X**				
Carboplatin AUC = 6 [7]		**X**				

1) Abbreviations: H&P=History and Physical examination; PS=ECOG performance status; VS=vital signs (blood pressure, temperature, pulse and respiratory rates, weight and height); TOX=toxicity assessment; CBC/diff=complete blood count and white blood cell differential; CMP=12 item complete metabolic profile (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, AST, ALT, total bilirubin, uric acid); UA=urinalysis; Pregnancy test only for women of childbearing potential

2) Baseline studies are repeated on day 1 if there are more than 14 days between baseline and day 1. The radiographic assessment must be repeated if there are more than 21 days between baseline and day 1.

3) TA= Tumor assessment by RECIST Criteria by diagnostic CT scan and/or MRI scan.

4) Day 1 and Days 2, 9 and 16 before each PF-05212384 dose

5) Days 2, 9 and 16 of the first cycle only, after each PF-05212384 dose

6) Dose is determined by the dosing cohort that the subject is enrolled into

7) The carboplatin dose (mg) = AUC x (CrCl + 25) where AUC = 6 depending on the dose level. The creatinine clearance will be calculated using a serum creatinine obtained within 3 days prior to each dose. Carboplatin dose will be based on GFR* (glomerular filtration rate) based on the measurement of creatinine clearance where GFR is calculated using the Cockroft-Gault Formula:

CrCI = [(140 - age) x actual body weight (kg)**] / [72 x serum creatinine***]

Multiply this number by 0.85 if the subject is female.

* GFR = calculated creatinine clearance determined using the Cockroft-Gault Formula based on age, weight (actual body weight) and serum creatinine.

** Use current (actual) weight. This should be actual weight but not exceed 140% of IBW.

*** In subjects whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing.

Please note that: GFR should not exceed 125 m/min. Hence, the maximum total carboplatin dose should NOT exceed 900 mg.

****Follow up evaluations are also performed as appropriate clinically

6.2 Screening Evaluations

Written informed consent must be obtained prior to performing any study-specific evaluations or tests. Tests or evaluations performed as standard of care within the specified screening period, but prior to informed consent, may be accepted for this study and need not be repeated.

Pretreatment measurements (to be completed within 21 days prior to initiation of therapy):

a. Height, weight and performance status
b. Physical exam
c. Laboratory studies:
    CBC with leukocyte differential count
    Comprehensive metabolic panel (CMP)
    Urine pregnancy test (females of potential child-bearing status only)
    Plain films, CT or PET/CT scans, or MRI scans used for tumor measurement

6.3 On-Study Evaluations

Prior to initiating each treatment cycle:

a. Toxicity assessment, interim medical history and physical examination
b. Laboratory studies:
    CBC with leukocyte differential count
    CMP

Prior to initiating every other treatment cycle:

    CT, PET/CT or MRI scans to document tumor status.

6.4 End of Treatment

Subjects should be seen in the clinic or contacted by telephone to determine if any serious or non-serious adverse events have occurred within 28 days (± 3 days) of termination of PF-05212384 dosing.

Follow-up Evaluation

Subjects will be followed for 28 days after completion of the last course of any therapy for the documentation of adverse events.

Off-therapy measurements:

a. Toxicity assessment, interim medical history and physical examination
b. Laboratory studies:
    CBC with differential count
    CMP

6.5 Follow up/Survival

Subjects will be seen in follow-up at least every three months for the first year after the initiation of therapy or until disease progression, or the date of death. Evaluation will consist of an interim medical history and a physical examination. Additional studies, such as labs (CBC and CMP), and

any X-rays, or CT, PET/CT, bone scans or MRI scans used in evaluation of response will be repeated as clinically indicated. Other studies, such as, biopsies, will be performed as clinically indicated.

7. CRITERIA FOR DISEASE EVALUATION

7.1 **Defintions**

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their dose of any of the three drugs in this study.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are considered measurable only if they have demonstrated growth after completion of the radiation therapy.

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 (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions. All 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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 only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods 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 and never more than 4 weeks before the beginning of the treatment.

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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). 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. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater

than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy or Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers. Tumor markers alone cannot be used to assess response. There are no validated tumor markers for NSCLC, and none are being evaluated here.

Cytology or Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is

mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

7.2 **Response Criteria**

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

For Subjects with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.				
** Only for non-randomized trials with response as primary endpoint.				

***	In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note:	Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response

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

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

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

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event

The term "adverse event" includes any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically significant (*e.g.*, that requires unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study).

The adverse event may be:

- A new illness/condition;
- Worsening of a sign or symptom of the condition under treatment, or of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term "adverse event."

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition(s) for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded as an adverse event and not the abnormal objective findings (*e.g.*, viral hepatitis will be recorded as the adverse event and not the transaminase elevation). If a definitive diagnosis is not available, then the sign(s) (*e.g.*, clinically significant elevation of transaminase levels) or symptom(s) (*e.g.*, abdominal pain) will be recorded as the adverse event.
Adverse events fall into the categories "serious" and "non-serious."

8.1.2 **Serious Adverse Event**

A serious adverse event is one that at any dose of the study drug or at any time during the period of observation:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. "Medically important" should be marked only if no other serious criteria are met.

An "unexpected SAE" is any SAE for which the nature, specificity or severity is not consistent with the currently known adverse event profile of the investigational agent(s).

NOTE: The following hospitalizations are not considered SAEs in UFHCC clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

Clarification of the difference in meaning between "severe" and "serious"
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Any grade ≥ 3 adverse event per CTCAE is generally considered severe AE. This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.1.3 Non-Serious Adverse Event

A non-serious adverse event is any adverse event not meeting any of the serious adverse event criteria.

8.2 Period of Observation

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue for 30 days after the last administration of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should notify the DISC of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

The investigator will begin collecting non-serious adverse event (NSAE) information once administration of the investigational product is initiated. This NSAE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Treated subjects, including those who were prematurely discontinued from the study, will be followed for any adverse events that occur during the study until 28 days following the last dose of study treatment (i.e., the Follow-up Visit). However, if another course of anti-cancer therapy is initiated prior to the 28-day follow-up period visit, collection of adverse events will no longer be performed, with the exception of events that may be possibly, probably, or definitely related to the investigational agent or are clinically significant.

8.3 Documenting and Reporting of Adverse Events by Investigator

All adverse events must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

Every attempt should be made to describe the adverse event in terms of a diagnosis that encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have adverse events, whether considered associated with the use of study drug or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

8.3.1 Assessment of Causal Relationship to Study Drug

The Investigator will provide an assessment of the potential causal relationship between adverse events and study medication by determining whether or not there is a reasonable possibility that the event was caused by the study medication. The relationship or association of the adverse event to the study medication will be characterized as not related, probably not related, possibly related, probably related, or related:

Not Related: There is not a temporal relationship to the study drug administration or the adverse event is clearly due only to the progression of the underlying disease state, intercurrent illness, concomitant medication, concurrent therapy or other known cause.

Probably Not Related: There is little or no chance that the study drug administration caused the adverse event; the event is most likely due to another competing cause, including intercurrent illness, progression or expression of the disease state, or a reaction to a concomitant medication or concurrent therapy appearing to explain the reported adverse event.

Possibly Related: The association of the adverse event with the study drug administration is unknown; however, the adverse event is not reasonably attributed to any other condition.

Probably Related: When a reasonable temporal relationship exists between the adverse event and the study drug administration; significant symptoms abate upon discontinuation of the study drug and there is a reasonable explanation based on known characteristics of the study drug and there is no clear association with preexisting disease or therapy, intercurrent illness, concurrent

therapy or other factor(s).

Related: When the adverse event is a known side effect of the study drug or there is a temporal relationship to the administration of the study drug; or the adverse event reappears upon re-administration of the study drug (rechallenge); or the significant symptoms of the adverse event abate upon discontinuation of the study drug (dechallenge).

8.3.2 Intensity of Adverse Events

The intensity of adverse changes in physical signs or symptoms will be graded according to the CTCAE version 4. For all other adverse events not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories:

Mild (Grade 1) – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Moderate (Grade 2) – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

Severe (Grade 3) – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.

Life-threatening (Grade 4) – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Death (Grade 5) – the event resulted in death.

8.3.3 Action Taken with Study Drug

The action the Investigator took with study drug as a result of the event should be recorded as one of the following:

None – No action was taken with regard to the study drug as a result of the adverse event.

Interrupted – Study drug was stopped due to the adverse event, but was later resumed at the same dose.

Dose decreased – The dose of study drug was decreased as a result of the adverse event.

Permanently discontinued – The subject was withdrawn from the study due to the adverse event.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry:

Discontinued > dose decreased > therapy interrupted.

8.3.4 **Definition of Outcome**

The outcome of the AE should be recorded as one of the following:

Resolved without sequelae – The subject fully recovered from the adverse event with no observable residual effects.

Resolved with sequelae – The subject recovered from the adverse event with observable residual effects.

Not resolved – The adverse event was present at the time of last observation.

Death – The subject died as a result of the adverse event.

8.4 **Immediately Reportable Events**

8.4.1 **Serious Adverse Events**

For Pfizer reporting requirements, all SAEs, as well as exposure during pregnancy, must be reported to the Pfizer U.S. Clinical Trial Department or designee within 24 hours of awareness. SAEs will be reported to Pfizer via fax at (866) 997-8322. A Pfizer Investigator Initiated Research Serious Adverse Event Report Form must be used to document and communicate the event to Pfizer. In the event an embryo or fetus has been exposed to the investigational agent, a Pfizer Exposure During Pregnancy (EDP) Supplement Form must accompany the Investigator Initiated Research Serious Adverse Event Report Form. All event reports are to be faxed with the Pfizer Reportable Event Fax Cover Sheet (US).

For UFHCC SAE reporting requirements the FDA MedWatch 3500A form is the required form for internal submissions. In addition to completing appropriate subject demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch 3500A form:

1. Treatment regimen (dosing frequency, combination therapy)
2. Protocol description (and number, if assigned)
3. Description of event, severity, treatment, and outcome, if known
4. Supportive laboratory results and diagnostics
5. Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B., initials, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report.) MedWatch 3500A forms may be reported to the FDA by phone at (800) 332-1088, via fax at (800) 332-0178, or online at www.fda.gov/medwatch/report.htm.

UF DISC Reporting Requirements

Serious adverse events (SAE's) must be documented on a SAE Report Form must be emailed to the UFHCC DISC Safety Team within **5 days** of discovery of the event. The original copy of the SAE Report and any email correspondence must be kept within the Trial Master File at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Follow-up information will be emailed or faxed to the UFHCC using the SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the participant continued or withdrew from study participation.

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

8.4.2 **Other Events Requiring Immediate Reporting**

All pregnancies, regardless of outcome, must be reported to the UFHCC DISC, including pregnancies that occur in the female partner of a male study subject. All pregnancies must be followed to outcome.

Although overdose (dose variance of >25%) and cancer are not always serious by regulatory definition, these events should also be reported to the DISC in an expedited manner. In case the overdose did not result in any adverse event, the Investigator should report this as “overdose, no adverse event” on the SAE form and provide the intended amount, as well as the actual amount, of drug administered. In the event of overdose or exaggerated response, appropriate supportive measures should be employed. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Pregnancies and overdoses should be documented and reported per the SAE reporting guidelines in section 8.4.1 above.

8.5 IND Safety Reports Unrelated to this Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

9. STATISTICAL METHODS

The sections below provide an overview of the statistical considerations and analyses.

9.1 Study Objectives

9.1.1 Primary

- To identify the maximum tolerated dose of PF-05212384 in combination with paclitaxel and carboplatin in subjects with NSCLC (Phase Ib)
- To document the response rate of subjects with NSCLC receiving PF-05212384 with paclitaxel and carboplatin, according to current RECIST criteria (Phase II)

9.1.2 Secondary

- To document the severity and reversibility of toxicities
- To estimate median duration of response
- To estimate progression-free survival for subjects on this trial with NSCLC treated with PF-05212384 in combination with paclitaxel and carboplatin
- To estimate the overall survival of subjects with NSCLC receiving PF-05212384 with paclitaxel and carboplatin

9.2 Sample Size Determination

The trial will enroll 41 total subjects, 12 in the phase Ib portion and up to 29 in the phase II portion. In the phase II portion of the study, so we are interested in evaluating the feasibility and safety of a regimen of weekly PF-05212384 in combination with paclitaxel and carboplatin administered to subjects with non-small cell lung cancer. To minimize the number of subjects exposed, the sample size will be determined by the anticipated response rate. A response rate of 20% or above to PF-05212384 in combination with paclitaxel and carboplatin will be of interest in subjects with previously-treated squamous cell lung cancer. To determine the appropriate sample size with an overall type I error of 0.05 and power 0.8, Simon's two-stage design (Simon, 1989) is used. The null hypothesis that the true response rate is 0.05 is tested against a one-sided alternative that the true response rate is bigger than 0.2. In the first stage, 10 subjects will be accrued. If there are no responses among these 10 subjects, the study will be stopped. Otherwise, 19 additional subjects will be accrued for a total of 29. The null hypothesis will be rejected if 4 or more responses are observed in 29 subjects. This design yields a type I error rate of 0.047 and power of 0.8 when the true response rate is 0.2. A subject is considered eligible for toxicity evaluation if they have

received at least one dose of PF-05212384, paclitaxel or carboplatin. A subject will be considered eligible for evaluation of activity if they have also received two cycles of therapy as planned.

The phase Ib portion of the study will utilize a 3+3 dose escalation design using the dose levels of PF-05212384 listed in the table below. The doses for paclitaxel (200 mg/m^2, Q21 days) and carboplatin (AUC=6, Q21 days) do not adjust as part of the study design.

Dose Cohort	PF-05212384 Dose (mg, days 2, 9, 16)
1	110
2	150
3	180

During the first stage, cohorts of 3 participants each will be sequentially enrolled to each increasing dose level, beginning with dose level 2 (150mg) until the first dose limiting toxicity occurs. Once that happens, the first stage will end and the trial will move to the second stage. During the second stage, 10 subjects will be evaluated for response, and if none of the 10 evaluable subjects experiences a partial or complete response, then the study will be terminated. Otherwise, 19 additional subjects will be accrued for a total of 29. The null hypothesis will be rejected if 4 or more responses are observed in 29 subjects.

9.3 **Statistical Analysis Plan**

The maximum tolerated dose of PF-05212384, in combination with paclitaxel and carboplatin, will be determined by the dose escalation rules summarized in Sections 4.2 and 9.2. All subjects who received study drug will be included in the safety analysis of this combination regimen. Adverse event data and corresponding toxicity grades during treatment and during long-term follow-up will be summarized in the form of tables. Incidence tables will be generated to summarize incidence of subjects reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be displayed. Listings of adverse events by subjects will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. Safety data will be summarized for the overall subject group and by dose levels. Dose-toxicity curves will be fitted to the final data to estimate the toxicity rates of each dose levels.

9.4 **Efficacy Analysis**

The primary endpoint of the phase Ib portion of this protocol is to determine a tolerable phase II dose of PF-05212384 in combination with paclitaxel and carboplatin. The primary endpoint of the phase II portion of this study is to determine the objective response rate of disease to the administration of PF-05212384 in combination with paclitaxel and carboplatin. A secondary endpoint of this study will be progression-free survival following PF-05212384 therapy. Kaplan-Meier mean estimates and survival curves of progression-free survival rates will be calculated.

Secondary endpoints, including response rates, clinical benefit rate (CR + PR + SD), toxicities and reversibility of toxicities, will be estimated along with exact 95% binomial confidence intervals.

9.5 **Analysis of Demographic and Baseline Characteristics**

The analysis of demographic characteristics (age, gender, tobacco abuse history and ethnicity) and baseline characteristics, including weight, performance status, and histologic subtype, will be primarily descriptive. They will be summarized in tabular format.

9.6 **Analysis of Safety Data**

Subjects will be examined and graded each cycle for subjective/objective evidence of developing toxicity according to NCI-CTC toxicity criteria. Toxicities will be graded according to Common Toxicity Criteria (CTCAE) v4.03. Incidence tables will be generated to summarize incidence of subjects reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal, and incidence of serious adverse events.

In the absence of significant treatment-related abnormalities, in subsequent courses subjects will not require weekly laboratory evaluation, but will require the documentation of return to baseline values prior to the initiation of subsequent courses of therapy.

10. DATA AND SAFETY MONITORING

10.1 **Data Integrity and Safety Committee**

This protocol will be reviewed and monitored by the University of Florida Health Cancer Center (UFHCC) Data Integrity and Safety Committee (DISC) in accordance with their policies and procedures. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise; the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCC DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the sponsor-investigator of recommended action
- Notification of sites coordinated by the UFHCC of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

10.2 **On-Site Monitoring**

UFHCC monitors will make monitoring visits to the trial sites periodically during the trial to determine if sites are complying with the protocol. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The site investigator/institution guarantee access to source documents by UFHCC or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by any collaborating sponsors or their designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

10.3 **Principal Investigator Responsibilities**

As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.

The PI will be primarily responsible for monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper adverse event (AE) forms, CRFs, and Informed Consent forms.

11. EMERGENCY PROCEDURES

11.1 **Emergency Contact**

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol

.

11.2 **Emergency Identification of Investigational Products**

This is an unblinded, nonrandomized study. Thus, there will be no need for unmasking procedures, and the identification of the investigational product can be made by simple inquiry to the investigational pharmacy.

11.3 **Emergency Treatment**

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

12. ADMINISTRATIVE CONSIDERATIONS

12.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co-Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board (IRB) approval before initiation of the study.

The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

All potential serious breaches must be reported to the UF Health Cancer Center Data Integrity and Safety Committee (DISC) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

12.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB with reports, updates, and other information (e.g., amendments, and administrative letters) according to regulatory requirements or institution procedures.

12.3 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The Principal Investigator will maintain a list of Co-Investigators and other appropriately qualified persons to whom he has delegated significant study-related duties.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

12.4 Subject Information and Informed Consent

Before being enrolled in this clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language understandable to the subject and must specify the person who obtained informed consent.

After reading the informed consent document, the subject must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The subject's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the subject.

The PI will retain the original signed consent document. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

12.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Subjects will be told that the IRB, UF Health Cancer Center Data Integrity and Safety Committee, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

12.6 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the study protocol.

12.7 Case Report Forms

An electronic case report form (eCRF) is required and must be completed for each included subject. The completed dataset is the sole property of UFHCC and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from UFHCC.

12.8 **Record Retention**

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

UF Health Cancer Center requires that all study documentation be maintained for at least 6 years from the date of final study publication. No study records may be destroyed without prior authorization from UF.

13. REFERENCES

Jackman DM, Yeap BY, Sequist LV, et al. Exon 19 Deletion Mutations of Epidermal Growth Factor Receptor Are Associated with Prolonged Survival in Non-Small Cell Lung Cancer Patients Treated with Gefitinib or Erlotinib. Clin Cancer Res 2006;12:3908-14.

Rosell R, Taron M, Reguart N, et al. Epidermal Growth Factor Receptor Activation: How Exon 19 and 21 Mutations Changed Our Understanding of the Pathway. Clin Cancer Res 2006;12(24):7222-31.

Scagliotti GV, Parikh P, von Pawel J, et al. Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer. J Clin Oncol July 20, 2008; 26(21): 3543 - 3551.

Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. Oncologist 2009;14:253–263.

Sheng H, Shao J, Townsend CM Jr, Evers BM. Phosphatidylinositol 3-kinase mediates proliferative signals in intestinal epithelial cells. Gut 2003 Oct;52(10):1472-8.

Kim S, Domon-Dell C, Wang Q, et al. PTEN and TNF-alpha regulation of the intestinal-specific Cdx-2 homeobox gene through a PI3K, PKB/Akt, and NF-kappaB-dependent pathway. Gastroenterology 2002 Oct;123(4):1163-78.

Itoh N, Semba S, Ito M, et al. Phosphorylation of Akt/PKB is required for suppression of cancer cell apoptosis and tumor progression in human colorectal carcinoma. Cancer 2002 Jun 15;94(12):3127-34.

Jiang BH, Liu LZ. PI3K/PTEN signaling in angiogenesis and tumorigenesis. Adv Cancer Res 2009;102:19-65.

Ikezoe T, Nishioka C, Bandobashi K, et al. Longitudinal inhibition of PI3K/Akt/mTOR signaling by LY294002 and rapamycin induces growth arrest of adult T-cell leukemia cells. Leuk Res 2007 May;31(5):673-82. Epub 2006 Sep 27.

Powis, G., Bonjouklian, R., Berggren, et al. Wortmannin, a potent and selective inhibitor of phosphatidylinositol-3- kinase. Cancer Res 1994; 54:2419-23

Guertin DA, Sabatini DM. An expanding role for mTOR in cancer. Trends Mol Med 2005 Aug;11(8):353-61.

Mayer C, Grummt I. Ribosome biogenesis and cell growth: mTOR coordinates transcription by all three classes of nuclear RNA polymerases. Oncogene. 2006 Oct 16;25(48):6384-91.

Iadevaia V, Huo Y, Zhang Z, Foster LJ, Proud CG. Roles of the mammalian target of rapamycin, mTOR, in controlling ribosome biogenesis and protein synthesis. Biochem Soc Trans 2012 Feb 1;40(1):168-72.

Carson JD, Van Aller G, Lehr R, et al. Effects of oncogenic p110 alpha subunit mutations on the lipid kinase activity of phosphoinositide 3-kinase. Biochem J 2008;409:519-524.

Chaft JE, Arcila ME, Paik PK, Lau C, Riely GJ, Pietanza MC, Zakowski MF, Rusch V, Sima CS, Ladanyi M, Kris MG. Coexistence of PIK3CA and other oncogene mutations in lung adenocarcinoma-rationale for comprehensive mutation profiling. Mol Cancer Ther. 2012 Feb;11(2):485-91. doi: 10.1158/1535-7163.MCT-11-0692. Epub 2011 Dec 1.

Tang JM, He QY, Guo RX, Chang XJ. Phosphorylated Akt overexpression and loss of PTEN expression in non-small cell lung cancer confers poor prognosis. Lung Cancer. 2006 Feb;51(2):181-91.

Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet 2006;7:606-619.

Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signaling controls tumor cell growth. Nature 2006;441:424-430.

Alessi DR, James SR, Downes CP. Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Bα. Curr Biol 1997;7:261–269.

Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science 2005;307:1098–101.

Gingras AC, Kennedy SG, O'Leary MA, Sonenberg N, Hay N. 4E-BP1, a repressor of mRNA translation, is phosphorylated and inactivated by the Akt(PKB) signaling pathway. Genes Dev 1998;12:502-513.

Altomare DA, Testa JR. Perturbations of the AKT signaling pathway in human cancer. Oncogene 2005;24:7455–7464.

Fulton D, Gratton JP, McCabe TJ, et al. Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. Nature 1999;399:597-601.

Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature 1995, 378:785-789.

Maira SM, Stauffer F, Brueggen J, et al. Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. Mol Cancer Ther. 2008;7:1851-1863.

Tewari M, Quan LT, O'Rourke K, et al. Yama/CPP32 beta, a mammalian homolog of CED 3, is a CrmA-inhibitable protease that cleaves the death substrate poly(ADP-ribose) polymerase. Cell 1995;81:801 809.

Redfern WS, Carlsson L, Davis AS, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovasc Res 2003;58(1):32-45.

Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006 Dec 14;355(24):2542-50.

Evans WK, Earle CC, Stewart DJ, et al. Phase II study of a one hour paclitaxel infusion in combination with carboplatin for advanced non-small cell lung cancer. Lung Cancer 1997 Aug;18(1):83-94.

Shapiro GI, Bell-McGuinn KM, Molina JR, et al. First-In-Human Study of PF-05212384 (PKI-587), a Small-Molecule, Intravenous, Dual Inhibitor of PI3K and mTOR In Patients With Advanced Cancer. Clin Cancer Res. 2015 April 15; 21(8): 1888–1895. doi:10.1158/1078-0432.CCR-14-1306.

APPENDIX
PERFORMANCE STATUS CRITERIA

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