PHASE 1B/2 STUDY OF PF-04136309 IN COMBINATION WITH GEMCITABINE AND NAB-PACLITAXEL IN PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA

Compound:	PF-04136309
Compound Name:	Not Applicable (NA)
United States (US) Investigational New Drug (IND) Number:	128040
European Clinical Trials Database (EudraCT) Number:	2015-003767-11
Protocol Number:	A9421018
Phase:	1b/2

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	09 November 2015	Not applicable (N/A)
Amendment 1	25 November 2015	• Added the EORTC QLQ-CIPN20 questionnaire to be collected on Cycle 1 Day 1 (baseline), Day 1 for all subsequent cycles, End of Treatment (EOT) and at the Follow-up visits. • Added Section 7.1.5 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20). • Added Secondary Objective to evaluate to evaluate the improvement of peripheral neurotoxicity induced by nab-paclitaxel by the addition of PF-04136309 to the combination therapy of nab-paclitaxel plus gemcitabine. • Added Secondary Endpoint to evaluate Peripheral neurological adverse events as characterized by frequency, severity (as graded by NCI CTCAE v.4.03 and by self-assessment according to the EORTC QLQ-CIPN20 questionnaire), and timing. • Clarified Study Overview for Phase 1b – Section 3.1. • Clarified dose finding and stopping rules – Study Design Section, and Section 3.2 Study Design and Stopping Rules (Phase 1b). • Added Section 3.4 – Late Onset Toxicity and Toxicities.

Document	Version Date	Summary of Changes and Rationale
		• Corrected typo in Section 9.1.3 – Analysis Set numbering [4. Per protocol analysis set…] • Corrected Section 9.2.2 – Statistical Methods for Dose Escalation/De-Escalation (Phase 1b) [Target size for each cohort will be n=2 to 4 patients….] • Corrected Section 3.3 – Dose Limiting Toxicities. Subjects are planned to be enrolled in cohorts of 2 to 4 subjects. • Section 9.6.3 renamed as section 9.6.2.1. • Section 9.6.2.2 added: Analysis of Peripheral Neurological Adverse Events and of the EORTC QLQ-CIPN20 Questionnaire. • Added a footnote for clarification purposes for TABLE 11. • Section 5.1.2 corrected randomization ratio to 1:1.

Amendment 2	30 September 2016	• Incorporated Protocol Administrative Clarification Letters (PACL):
		
		  • PACL #1 12Jan2016:
		
		  • Updated Table 1 Footnote 27 (formally footnote 25), Table 2 *deleted footnote 7*, and Section 7.5 with an additional banked blood biospecimen added at C3D1. Collection should be at Screening and pre-dose C3D1.

Document	Version Date	Summary of Changes and Rationale
		• PACL #2 27Jan2016: • Clarification in Table 1 and Section 7.1.4 - Weight is collected when the Physical Examination is performed: Screening, each Cycle on Days 1, 8, and 15, and at the EOT and Follow-up Visits. • Background and Rationale (Protocol Summary) and Section 1.2.1 Study Rationale - This clarification provides background and rationale for how CCR2 in primary sensory neurons contributes to paclitaxel-induced peripheral neuropathy. • Section 7.1.3.1 Hematology and Blood Chemistry and Table 6 (formally Table 9) - This clarification is being provided to remove the reference to Day 0 collection in footnote c, as well as delete the urine drug collection at screening. Both items were errors and should be removed from the protocol. • This clarification was provided to remove incorrect footnote text for Banked Biospecimens in Table 1 and replace with the correct consistent text for Banked Biospecimens. Collection of the banked biospecimens at Screening and C3D1 pre-dose.

Document	Version Date	Summary of Changes and Rationale
		• The following clarification was made to remove any reference to the term "legally acceptable representative" in the protocol Section 8.13 Eliciting Adverse Event Information, and Section 12.3 Patient Information and Consent. • Correction in Section 9.3 Sample Size Determination - This clarification is provided to correct a typographical error. New Text: Phase 2: Ninety-two (92). • PACL #3 11Feb2016: • Clarification to remove the "(X)" mark for triplicate 12-lead ECG activity (assessment) at the Follow-up Visit. • Clarification in Schedule of Activities Table 1, Section 1.2.2, and Section 7.1.5: EORTC QLQ-C30 in combination with QLQ-CIPN20: Questionnaires will be completed prior to any study or medical procedure on Cycle 1 Day 1 (-2 day window), Day 1 of all subsequent cycles, and at the End of Treatment visit. One final questionnaire will be completed 4 weeks after discontinuation of IP during the Follow-up Visit. • PACL #4 01Mar2016: • This administrative clarification is provided to remove the "3" under

Document	Version Date	Summary of Changes and Rationale

		subsequent cycles. Schedule of Activities (SOA) Table 2 has been corrected to properly reflect the RNA Profiling (whole blood) is collected on pre-dose Day 1, 2, 8, and 15 of Cycle 1, Day 1 (pre-dose) of Cycles 2, 4, 7 and at End of Treatment. The collection noted for Cycle 3 has been removed and the table now aligns with Table 2 – Footnote #4.
		• PACL #5 20May2016:
		  • Remove the secreted protein acidic and rich in cysteine (SPARC) blood sample collection from the protocol. Rationale: no longer required.
		  • This administrative change and rationale is provided to clear up the inconsistency between the guidance in Table 4. Section 3.7.1: PF-04136309 does not have to be interrupted in case of hematologic toxicity or peripheral neurotoxicity with the exception for grade 4 hematological toxicity (see Table 4: Recommended Dose Modifications for Neutropenia and/or Thrombocytopenia). PF-04136309 should be interrupted in case of > Grade 2 non-hematologic or non-peripheral neurological toxicity, potentially due to PF-04136309.

Document	Version Date	Summary of Changes and Rationale
		• Remove all fasting requirement prior to PF-04136309 oral administration. Section 5.4.1. Rationale: There is no food effect on PF-04136309 based on the food effect study (A9421019). • Provision added for allowable treatment window for PF-04136309 as a result of the food effect study (A9421019) PK data. See section 5.4.1 and SOA Table 1 – Footnote 16. • Provision added for the Cycle 1 Day 1 12-hour post-dose collection to be "optional' for the target engagement ex-vivo inhibition of CCL2-induced, ERK phosphorylation by PF-04136309. See Table 2, Footnote 2. Rationale: Not a mandatory sample collection and 12-hour post dose is an extremely difficult time point for the patients on Day 1 of chemo. • Removed duplicate Tables, 6, 7, and 8 from Section 5.4.6. Please refer to the information in Tables 3, 4, and 5. Rationale: Clarification. • Updated Reference List – added 9 new references (#20-28). • Statistical Updates and Clarifications provided in the following sections for Phase 2: • Section 5.1.2 - Phase 2 Randomized.

Document	Version Date	Summary of Changes and Rationale
		• Table 6 – Change: added Total bile acids, Acetaminophen drug and/or protein adduct levels added for repeat potential Hy's law cases. Rationale: Additional tests were added in order to accurately conduct Hy's Law assessments. • Section 9.1.3 – Analysis Sets. • Section 9.4.2 – Analysis of Objective Overall response (ORR: CR or PR). • Section 9.4.3 – Analysis of Duration of Objective Response (DR). • Section 9.5.1 – Analysis of PF-04136309 Pharmacokinetics. • Section 9.6.2.2 – Analyses of Peripheral Neurological Adverse Events, EORTC QLQ-C30 and QLQ – CIPN20 Questionnaires. • All other changes are minor in nature added to this amendment to provide clarity and additional information.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

ABBREVIATIONS

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Ab	Antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BMA	bone marrow aspirate
BP	blood pressure
BSS	Baseline signs and symptoms
BUN	blood urea nitrogen
C	Cycle
C	Concentration
CA19.9	cancer antigen 19.9
CCL	chemokine ligand
CCL2	chemokine ligand-2 (JE-1, MCP-1)
CCR	chemokine receptor
CCR1	chemokine (C-C motif) receptor 1
CCR2	chemokine (C-C motif) receptor 2
CCR5	chemokine (C-C motif) receptor 5
CDS	core data sheet
CHF	congestive heart failure
CI	confidence interval
CIPN	Chemotherapy induced peripheral neuropathy
CL	Clearance
Cmax	maximum observed concentration
CNB	core needle biopsy
CNS	central nervous system
CR	complete response
CRF	case report form
CRM	Continuous Reassessment Method
CSA	clinical study agreement
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
D	Day
DAI	dosage and administration instructions
DEHP	di-(2-ethylhexyl)phthalate
DICOM	Digital Imaging and Communications in Medicine
DLT	dose-limiting toxicity
DMC	data monitoring committee

Abbreviation	Term
DNA	deoxyribonucleic acid
DR	Duration of Response
EC	ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eg	for example
EORTC QLQ-CIPN20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire is a questionnaire developed to assess the quality of life of cancer patients (30 questions)
EOT	End of Treatment
ERK	extracellular signal regulated kinase
etc	'and other things' or 'and so forth'
EudraCT	European Clinical Trials Database
5-FU	Fluorouracil
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	formalin-fixed paraffin-embedded
FNA	fine-needle aspirate
FOLFIRINOX	chemotherapy regimen made up of the following four drugs: fluorouracil [5-FU], leucovorin, irinotecan, oxaliplatin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCT	Hematocrit
HCV	hepatitis C virus
HDPE	high-density polyethylene
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	Identification
ie	that is
IgA	immunoglobins A
IgG	immunoglobins G
IgM	immunoglobins M
IL	Interleukin
IM	inflammatory monocytes
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review board
IUD	intrauterine device
IV	Intravenous
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LFT	liver function test

Abbreviation	Term
LPD	local product document
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
mTPI	modified toxicity probability interval
MD	multiple dose
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval method
N/A	not applicable
NCI	National Cancer Institute
OA	Osteoarthritis
OBD	optimal biological dose
ORR	objective response rate
OS	overall survival
pT	target probability
PCD	primary completion date
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetics
PK/PD	pharmacokinetics/pharmacodynamics
PLT	Platelet
PMAP	Population Modeling Analysis Plan
PMAR	Population Modeling and Analysis Report
PO	Oral
POM	proof of mechanism
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
QD	every day
QRS	Name for the combination of three of the graphical deflections seen on a typical electrocardiogram (EKG or ECG).
QT	time between the start of the Q wave and the end of the T wave
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's corrections
R	Ratio
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	single dose
SIB	suicidal ideation and behavior
SPC	Summary of Product Characteristics
SRSD	single reference safety document

Abbreviation	Term
T	time
$T_{1/2}$	terminal elimination half-life
T(cell)	thymic origin lymphocytes that have a central role in cell mediated immunity
TAM	tumor associated macrophages
TBIL	total bilirubin
TBR	tumor background ratio
TCR	T cell receptor
TE	target engagement
TGFβ	tumor growth factor beta
TILs	tumor infiltrating lymphocytes
T_{max}	time to first occurrence of C_{max}
TTP	time to progression
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USPI	United States Package Insert
UVB	ultraviolet B light
V	volume of distribution
vs	versus
V_{ss}	steady state volume of distribution
WBC	white blood cell count

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

PROTOCOL SUMMARY

Background and Rationale:

Progress in basic and translational immunology has confirmed the importance of the immune system in cancer progression and in its treatment and has renewed interest in immune-based therapy for cancer, including pancreatic cancer. The main cellular components contributing to the immunosuppressive microenvironment include myeloid-derived suppressor cells (MDSC), tumor associated macrophages (TAM), mast cells, and T regulatory cells (Treg).[1,2] Of these, MDSC comprise a heterogeneous population of the immature cells arising from the myeloid lineage, and they are considered to be the key in orchestrating the suppressive tumor microenvironment. Myeloid-derived suppressor cells are increased in many pathological conditions such as infections, inflammatory disease, sepsis, traumatic shock, and pancreatic cancer.[3,4] Myeloid-derived suppressor cells are observed with increased prevalence in the peripheral blood and in the tumor microenvironment of patients with solid tumors, including pancreatic cancer.[5] Moreover, the number of circulating MDSC significantly correlates with clinical state and metastatic tumor burden[6], and elimination of MDSC has been shown to improve antitumor activity.[7,8,9,10] Because MDSC are proven to be one of the main mechanisms of tumor evasion from the immune system, the pharmacological modulation of MDSC and prevention of their appearance or infiltration to solid tumors represent potential novel and innovative therapeutic strategies in cancer.[9,11,12,13,14,15,16]

While the mechanisms responsible for MDSC expansion and trafficking to tumors is not entirely understood, it has been shown that MDSCs express Chemokine (C-C motif) receptor 2 (CCR2) and that the Chemokine (C-C motif) ligand 2 (CCL2)/CCR2 signaling axis contributes to tumor progression through the CCR2 mediated MDSC recruitment and/or accumulation.[17,18,19]

PF-04136309 is an orally active CCR2 antagonist. It is selective for CCR2 against a panel of human chemokine receptors. When evaluated against human monocytes and human whole blood, PF-04136309 blocked CCR2 mediated signal transduction, chemotaxis and CCL2 binding at similar concentrations. While initially developed for the treatment of acute and chronic pain and liver fibrosis, the focus of development is now on oncological indications.

Not only do MDSCs express the chemokine receptor CCR2, but in murine models of pancreatic cancer, it has been shown that MDSCs are upregulated in the tumor bearing host, promote tumor growth, suppress antitumor immunity and when depleted result in increased survival.[5] Additionally it has been shown that CCR2 is upregulated on MDSC in both the circulation and tumor and that PF-04136309 can effectively block MDSC recruitment resulting in significantly reduced tumor growth.

Based on these findings it is hypothesized that CCR2 may be a promising therapeutic target in pancreatic cancer, a tumor associated with a marked up regulation of MDSCs in the tumor microenvironment in both mouse models and human patients.

Beside the potential interest in terms of anti-tumor efficacy, the expression of CCL2 and CCR2 is upregulated by dorsal root ganglia neurons in rodent models of neuropathic pain. CCL2 increases the excitability of nociceptive neurons after a peripheral nerve injury, and disruption of CCL2 signaling blocks the development of neuropathic pain.[20] Furthermore, several authors reported that induction of CCL2 and its receptor CCR2 in primary sensory neurons contributes to paclitaxel-induced peripheral neuropathy (CIPN).[21,22] Activation of paracrine CCL2/CCR2 signaling between dorsal root ganglion neurons plays a critical role in the development of paclitaxel-induced peripheral neuropathy. Preclinically, paclitaxel induces increased expression of CCL2 in spinal astrocytes. Local blockade of CCL2/CCR2 signaling by anti-CCL2 antibody or CCR2 antisense oligodeoxynucleotides significantly attenuates paclitaxel CIPN phenotypes including mechanical hypersensitivity and loss of intraepidermal nerve fibers in hindpaw glabrous. Targeting CCL2/CCR2 signaling could be a novel therapeutic approach.[22] A potential beneficial effect of PF-04136309 on paclitaxel-CIPN will be assessed through European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC CIPN20) questionnaire[23,24,25,26,27] and National Cancer Institute Common Terminology Criteria For Adverse Events (NCI-CTC AE).[25,26,27,28]

Complete information for PF-04136309 may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.

The SRSD for Gemcitabine (Gemzar®) is the Eli Lilly United Kingdom (UK) Summary of Product Characteristics (SmPC).

The SRSD for nab-paclitaxel (Abraxane®) is the US Package Insert (USPI).

Biomarker Rationale:

The objective of biomarker collections and analyses is to provide evidence of target engagement (TE), pharmacodynamic activity and proof of mechanism (POM) of PF-04136309 in combination with nab-paclitaxel + gemcitabine. This will provide data to inform dose selection, characterize the relationship between PF-04136309 TE, pharmacodynamic activity, and any observed anti-tumor effects. Furthermore, this may enable the identification of patients and/or tumor phenotypes most likely to respond to PF-04136309, nab-paclitaxel + gemcitabine combination therapy.

Target engagement will be assessed using a flow cytometry assay to measure the inhibition of extracellular signal regulated kinase (ERK) kinase phosphorylation in whole blood samples exposed to the CCR2 ligand, CCL2, ex vivo. If sufficient data is collected to characterize TE at the Recommended Phase 2 Dose (RP2D) in Phase 1b, this assessment will not be included in Phase 2 of the study.

Tumor-associated macrophages (TAMs), of which MDSCs are an important subset, have been shown to support both primary tumor survival and eventual metastases by inhibiting anti-tumor immunity, establishing a toleragenic microenvironment and seeding sites of metastases.[20,30,31] Tumor-associated macrophages are derived from CD14+CCR2+ inflammatory monocytes (IMs) which leave the bone marrow and traffic to the tumor and

sites of metastases in response to production of the CCR2 ligand, chemokine ligand-2 (CCL2).[32] Once resident in this tissue, these monocytes convert to a TAM phenotype which inhibits anti-tumor T cell activity and promotes the shift to a toleragenic tumor microenvironment.[33,34] Inhibition of CCR2 activity by PF-04136309 has been shown in pre-clinical and clinical studies to increase the ratio of IMs in the bone marrow to that in the peripheral blood, deplete TAMs from primary tumors and inhibit metastases to lung and liver.[39] Evidence for this mechanism being active during PF-04136309, nab-paclitaxel + gemcitabine combination therapy will be provided by measurement of IM and TAM in the peripheral blood, bone marrow aspirates and fine-needle aspirates (FNAs) or core needle biopsy of metastases and/or primary tumor by flow cytometry.

Accumulation of the CCR2 ligand, CCL2, has been associated with a rebound of metastases after cessation of antibody-mediated blockade of CCR2 in pre-clinical breast cancer models.[38] Plasma samples will be collected and analyzed for CCL2, cytokines and chemokines by immunoassay to monitor for CCL2 accumulation and potential effects on adaptive immunity.

Study Objectives and Primary Endpoint:

Objectives:

Phase 1b Dose Finding Objectives

Primary Objectives

- To evaluate the safety and tolerability of PF-04136309 in combination with nab-paclitaxel + gemcitabine in patients with metastatic pancreatic ductal carcinoma.

- To characterize the dose limiting toxicities (DLTs) and overall safety profile of escalated doses of PF-04136309 and the associated schedule.
- To determine the maximum tolerated dose (MTD) of PF-04136309 and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives

- To evaluate the pharmacokinetics (PK) of PF-04136309 when given in combination with nab-paclitaxel + gemcitabine in combination.
- To characterize the ex vivo inhibition of CCL2-induced ERK kinase phosphorylation as a measure of target engagement following treatment with PF-04136309 in combination with nab-paclitaxel + gemcitabine at each dose level.

CCI

Phase 2 Randomized Double Blinded Placebo Control Study

Primary Objective

- To assess the enhancement of efficacy of PF-04136309 in combination with nab-paclitaxel + gemcitabine versus nab-paclitaxel + gemcitabine + placebo in terms of progression free survival (PFS).

Secondary Objectives

- To assess the enhancement of efficacy of PF-04136309 in combination with nab-paclitaxel + gemcitabine versus nab-paclitaxel + gemcitabine + placebo in terms of Overall Survival (OS).
- To assess the enhancement of efficacy of PF-04136309 in combination with nab-paclitaxel + gemcitabine versus nab-paclitaxel + gemcitabine + placebo in terms of Objective Response Rate (ORR) and duration of response.
- To evaluate the safety and tolerability of PF-04136309 in combination with nab-paclitaxel + gemcitabine.
- To evaluate the population PK of PF-04136309 given in combination with nab-paclitaxel + gemcitabine.
- To validate the proof of mechanism of PF-04136309 in combination with nab-paclitaxel + gemcitabine compared to nab-paclitaxel + gemcitabine + placebo.
- To evaluate to evaluate the improvement of peripheral neurotoxicity induced by nab-paclitaxel by the addition of PF-04136309 to the combination therapy of nab-paclitaxel + gemcitabine.

CCI

- [redacted]
- [redacted]
- [redacted]

[redacted]

Endpoints

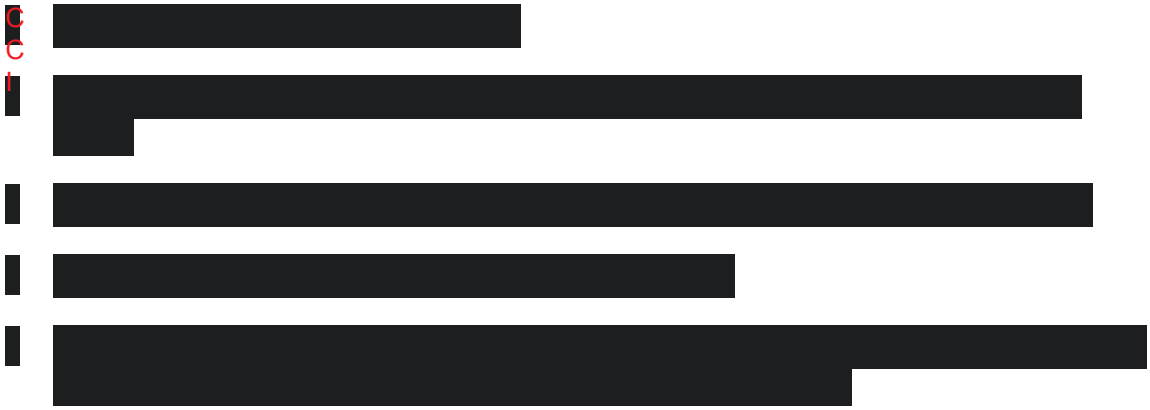
Phase 1b Dose Finding Endpoints

Primary Endpoint

- Dose Limiting Toxicities (DLTs) in order to determine the MTD and RP2D.
- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03) timing, seriousness and relationship to study therapy.
- Lab abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) and timing.

Secondary Endpoints

- PK parameters of PF-04136309 after multiple dosing, including $C_{max,ss}$, T_{max}, $AUC_{tau,ss}$, $C_{min,ss}$, CLss/F, and as data permit, $t_{1/2}$ and Vss/F.
- Ex vivo inhibition of CCL2-induced ERK kinase phosphorylation in the peripheral blood.



Phase 2 Randomized Study

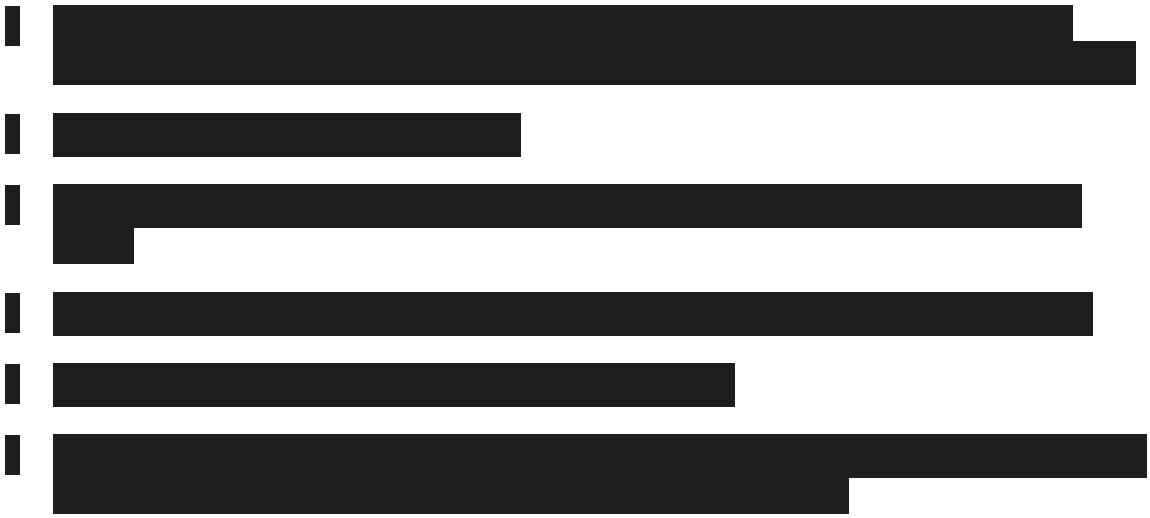
Primary Endpoint

- Progression Free Survival (PFS).

Secondary Endpoints

- Overall Survival (OS).
- Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study treatment.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.
- Objective response rate (ORR).
- Duration of Response. [The rate of progression-free survival at 1 year, the rate of disease control (confirmed response or stable disease for ≥16 weeks)].
- Time to progression with the double combination PF-04136309 + gemcitabine (maintenance therapy) after interruption of nab-paclitaxel.
- Trough PF-04136309 concentrations.
- Pharmacodynamic markers in metastatic tumors and bone marrow: Pre-biopsy – Post-biopsy after 1 or 2 cycles of PF-04136309 + nab-paclitaxel + gemcitabine or nab-paclitaxel + gemcitabine + placebo.
- Peripheral neurological adverse events as characterized by frequency, severity (as graded by NCI CTCAE v.4.03 and by self-assessment according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20)), and timing.

CCI [redacted]



Study Design

This is a multi-center Phase 1b/2 study in the first-line treatment of patients with metastatic pancreatic ductal adenocarcinoma (mPDA).

The Phase 1b will be open label as patients will receive ascending doses of PF-04136309 in combination with nab-paclitaxel + gemcitabine. The phase 2 will be controlled, randomized and double blinded as patients will be randomized to receive PF-04136309 in combination with nab-paclitaxel + gemcitabine (ARM A) versus nab-paclitaxel + gemcitabine + placebo (ARM B).

-Phase 1b study: Open label dose finding.

This study will include a dose finding phase. In the dose finding phase, patients will be enrolled in cohorts of 2 to 4 patients, starting with 750 mg BID of PF-04136309. A new cohort of n=2 to 4 patients exposed to the same dose 750 mg twice daily (BID) could be opened after safety has been established for at least the first cycle in all patients in the previous cohort. Escalation to a higher dose (eg 1000 mg BID) will require that at least n=6 patients are dosed at 750 mg BID and no more than 1 experienced a DLT.

An MTD may not be identified, as DLTs may not be observed after administration of this investigational agent. Based on safety data, and, PK and PD data, dose escalation may continue up to a predefined Maximum Feasible Dose (ie, 1000 mg BID) or Phase 2 recommended dose.

Dose levels may include de-escalation (500 mg BID) if a high number of the patients (ie, >33%) receiving 750 mg BID experiences a DLT related to PF-04136309. Based on safety and other results (eg, PK) from patients enrolled in the dose escalation cohorts, a dose level will be selected to be further evaluated as the Recommended Phase 2 Dose (RP2D). A minimum of 6 to 12 patients will be treated at this dose level to establish it as the RP2D.

-Phase 2 study: Randomized double blinded placebo control.

Ninety-two patients will be randomized with a 1:1 to receive PF-04136309 in combination with nab-paclitaxel + gemcitabine (ARM A; n=46) versus nab-paclitaxel + gemcitabine + placebo (ARM B; n=46). Randomization will be stratified by site (two strata: the site of University of Rochester, and other sites).

The primary objective will be the enhancement of efficacy in terms of PFS.

In both studies, treatment may continue until progression of disease (PD) unacceptable toxicity or patient refusal, whichever comes first. After 6 months, in case of neurological or hematological chronic ≥ Grade 2 toxicity, nab-paclitaxel may be stopped and gemcitabine + PF-04136309 or gemcitabine + placebo will be continued until disease progression or patient's or investigator's decision. If gemcitabine is not well tolerated, treatment may be continued with PF-04136309 alone until disease progression or patient's or investigator's decision.

The proof of mechanism of action of PF-04136309 will be assessed by the comparison of at least 12 paired (optional) biopsies in each treatment arm, bone marrow aspirates and peripheral blood (pre- and post- treatment in the Phase 2 study). Their optional collection will provide baseline, pre-dose core needle biopsy or fine needle aspirate (only if a CNB sample collection from a metastatic site is not feasible) and/or bone marrow aspirates, and a core needle biopsy or FNA, and/or bone marrow aspirates following the completion of Cycle 1 at C1D28 [±7 days] or at C2D28 [±7 days] if collection at Cycle 1 is not obtained.

Serial blood samples will be collected from patients enrolled in the Phase 1b cohorts to determine the multiple dose PK of PF-04136309 given in combination with nab-paclitaxel + gemcitabine. Sparse PK sampling will be performed for patients enrolled in the Phase 2 portion of the study to evaluate the population PK of PF-04136309.

Study Treatment

Dose Rationale

PF-04136309 was studied in healthy subjects after a single oral dose over the dose range of 1 to 1000 mg, and after repeated oral administration at 5 to 500 mg twice daily (BID) for 14 consecutive days. These doses were generally safe and well tolerated with no dose limiting adverse events. Using phosphorylation of ERK (pERK) as a whole blood biomarker for the pharmacologic inhibition of CCR2 inhibition, these studies showed that PF-04136309 maximally suppressed pERK phosphorylation in whole blood monocytes for at least 12 hours at doses ≥150 mg, which suggest a complete or near complete saturation of circulating CCR2 at doses ≥150 mg BID.

PF-04136309 at a dose of 500 mg BID has been combined with FOLFIRINOX chemotherapy in a Phase 1/2 study[39] in 39 patients with borderline and locally advanced pancreatic cancer. The study design did include 6 patients treated with FOLFIRINOX alone. Comparison of toxicities between the 2 groups of patients showed that the combination of PF-04136309 and chemotherapy was well tolerated with most of the observed adverse events

being attributed to the chemotherapy. Also, it was observed that PF-04136309 at 500 mg BID inhibited the migration of IMs from the bone marrow to the tumor, and depleted tumor infiltrating regulatory T cells.

While the mechanisms responsible for MDSCs expansion and trafficking to tumors are not entirely understood, it has been shown that MDSCs express CCR2 and that the CCL2/CCR2 signaling axis contributes to tumor progression through the CCR2-mediated MDSC recruitment and/or accumulation. No data is available regarding the exposure-response relationship of PF-04136309 for CCR2 occupancy on MDSCs in the tumor.

Previous non-oncology and oncology studies have shown that repeated administration of PF-04136309 at 500 mg BID appears to be safe and pharmacologically active. Doses higher than 500 mg, (ie, 750 mg and 1000 mg) have been evaluated as single dose but not following repeated administration. In the phase 1 escalation phases, no DLTs have been reported and toxicities were mild.

Given the uncertainty whether the PF-04136309 exposure achieved after 500 mg BID dosing would be able to maximally occupy CCR2 in the tumor, the dose finding in the present study will start with the PF-04136309 dose of 750 mg BID, to be given in combination with nab-paclitaxel + gemcitabine. The PF-04136309 dose of 1000 mg BID is considered as the maximal feasible dose for the study. Strict de-escalation rules will apply and lower dose levels may be explored.

The PF-04136309 or placebo for this study will be oral administration twice a day for 28 consecutive days each cycle.

Nab-paclitaxel and gemcitabine will be administered according to the approved dosing schema in this indication.

In each cycle, nab-paclitaxel will be administered first as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 followed by 1 week of no treatment (Schedule 3/1). The dose of nab-paclitaxel will be 125 mg/m^2.

Gemcitabine will be administered immediately after nab-paclitaxel, as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each cycle, followed by 1 week of no treatment (Schedule 3/1). The dose of gemcitabine will be 1000 mg/m^2.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. Schedule of Activities for Phase 1b/2

	Screen[1] (≤28 days)	Cycle 1 (28 days)								Subsequent Cycles (28 Days)				End of Treatment (EOT)[28]	Follow-up[29]
Protocol Activity		**Day 1**	**Day 2**	**Days 3, 4**	**Day 8**	**Day 15**	**Day 16**	**Day 22**	**Day 28**	**Day 1**	**Day 8**	**Day 15**	**Day 28**		
Allowable Visit Window	**days**	**±1**	**±1**	**±1**	**-1 day/+3 days**	**-1 day/+3 days**	**±1**	**±3**	**±3**	**±3**	**-1 day/+3 days**	**-1 day/+3 days**	**±3 Scans ±7**	**±7**	**±7**
Informed Consent[2]	X														
Medical History[3]	X														
Physical Examination[4]/Vital Signs[6]	X	X			X	X				X	X	X		X	(X)
Baseline Signs and Symptoms[5]		X													
Height	X														
Weight	X	X			X	X				X	X	X		X	X
ECOG Performance Status[7]	X	X								X				X	
Laboratory Studies															
Hematology[8]	X	X			X	X		X		X	X	X		X	(X)
Blood Chemistry[9]	X	X			X	X		X		X	X	X		X	(X)
Coagulation[10]	X	X								X				X	(X)
Urinalysis[11]	X	X								X				X	(X)
Pregnancy Test[12]	X	X								X				X	(X)
Immunoglobulin (IgG, IgA, IgM)		X			X	X				X		X		X	(X)
Viral disease screen where required by regulations[13]	X														
12-lead ECG[14]	X	X		X (day 3 only)				X		X (C2, C3)				X	

Table 1. Schedule of Activities for Phase 1b/2

	Screen[1] (≤28 days)	Cycle 1 (28 days)								Subsequent Cycles (28 Days)				End of Treatment (EOT)[28]	Follow-up[29]
Protocol Activity		**Day 1**	**Day 2**	**Days 3, 4**	**Day 8**	**Day 15**	**Day 16**	**Day 22**	**Day 28**	**Day 1**	**Day 8**	**Day 15**	**Day 28**		
Allowable Visit Window	**days**	**±1**	**±1**	**±1**	**-1 day/+3 days**	**-1 day/+3 days**	**±1**	**±3**	**±3**	**±3**	**-1 day/+3 days**	**-1 day/+3 days**	**±3 Scans ±7**	**±7**	**±7**
Registration and Treatments															
Registration[15]	X														
PF-04136309[16]		Day 1 to Day 28								Day 1 to Day 28					
Nab-paclitaxel (Nab-P)[17]		X			X	X				X	X	X			
Gemcitabine (GEM)[18]		X			X	X				X	X	X			
Tumor Assessments															
CT or MRI Scans[19]	X (-7 days)												X (±7 days) To be assessed every 8 weeks – efficacy assessment starts at the end Cycle 2 Day 28 prior to start of Cycle 3	(X)	(X)
Other Clinical Assessments															
Adverse Events (AEs)[20]	X	X	X	X	X	X	X	X		X	X	X		X	X
Concomitant Medications[21]	X	X	X	X	X	X	X	X		X	X	X		X	X
Core Needle Biopsy from a Metastatic Site[22]	X								X (+/-7 days)				X (Day 28 +/- 7 days of Cycle 2, study day 56 only)	(X)	

Table 1. Schedule of Activities for Phase 1b/2

	Screen[1] (≤28 days)	Cycle 1 (28 days)								Subsequent Cycles (28 Days)				End of Treatment (EOT)[28]	Follow-up[29]
Protocol Activity		**Day 1**	**Day 2**	**Days 3, 4**	**Day 8**	**Day 15**	**Day 16**	**Day 22**	**Day 28**	**Day 1**	**Day 8**	**Day 15**	**Day 28**		
Allowable Visit Window	**days**	**±1**	**±1**	**±1**	**-1 day/+3 days**	**-1 day/+3 days**	**±1**	**±3**	**±3**	**±3**	**-1 day/+3 days**	**-1 day/+3 days**	**±3 Scans ±7**	**±7**	**±7**
Fine-needle Aspirate (FNA) of Primary Tumor (only if Core Needle Biopsy of a metastatic site not viable).[23]	X								X (+/-7 days)				+/- 7 days of Cycle 2, study day 56 only)		
Bone Marrow Aspirate (BMA)[24]	X								X [+/-7 days]				X (Day 28 +/- 7 of Cycle 2 (study day 56) only		
Blood for biomarker analyses[25]		See Pharmacokinetic (PK) and Pharmacodynamic Sampling Schedule Table 2 below													
Blood for PF-04136309 PK[26]		See Pharmacokinetic (PK) and Pharmacodynamic Sampling Schedule Table 2 below													
Retained Pharmacogenomic Blood Sample[27]	X									X (pre-dose C3D1 only)					
Serum for CA19-9		X								X				X	
Follow-up[29]															X
Survival[30]															X
Quality of Life Questionnaires (EORTC QLQ-C30 in combination with QLQ-CIPN20)[31]		X (-2 days)								X (C2, C3, C4, etc.)				X	X
Legend: (X) = Optional activity to be executed only if applicable. C = Cycle															

Abbreviations: AEs = adverse events; β-HCG=Beta Human Chorionic Gonadotropin; BMA=Bone Marrow Aspirate; C = cycle; CNB= Core Needle Biopsy; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; EORTC QLQ-CIPN20=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20; EOT = End of Treatment; FNA = fine needle aspiration; GEM = Gemcitabine; HbsAg=hepatitis B surface antigen; HbcAb=hepatitis B core antibody; HCVAb=Hepatitis C virus antibody; HIV=human immunodeficiency virus; IgA = Immunoglobulin A; IgG = Immunoglobulin G; IgM = Immunoglobulin M; MRI = magnetic resonance imaging; Nab-P = Nab-Paclitaxel; PK = pharmacokinetics; QLQ = Quality of Life Questionnaire

Footnotes (Schedule of Activities)

1. **Screening:** To be conducted within 28 days prior to treatment start.
2. **Informed Consent:** Must be obtained prior to undergoing any study specific procedures.
3. **Medical History:** To include date of diagnosis and information on prior anti-tumor treatments, surgeries, radiotherapy and recurrence date.
4. **Physical Examination:** Examination of major body systems including a neurological examination (See Appendix 5) and body weight. Height is measured at screening visit only. A neurological examination will be performed as part of the physical examination at Cycle 1 Day (prior to dosing), Day 1 on all subsequent cycles (prior to dosing), EOT, and at the Follow-up visit.
5. **Baseline Signs and Symptoms:** Patients will be asked about any signs and symptoms experienced within 14 days prior to study entry. Baseline signs and symptoms will be recorded on the Baseline Signs and Symptoms (BSS) Adverse Events case report form (CRF) page.
6. **Vital Signs:** Includes temperature, blood pressure (BP), and pulse rate (PR) to be recorded in the sitting position after approximately 5 minutes of rest.
7. **ECOG Performance Status:** ECOG performance scale is available in Appendix 3.
8. **Hematology:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. The list of required laboratory tests is provided in Section 7.1.3.1 Laboratory Safety Assessments.
9. **Blood Chemistry:** No need to repeat full blood chemistry on C1D1 if screening assessment performed within 7 days prior to that date. During Cycle 1, liver function tests, (AST, ALT, and bilirubin) must be checked on Days 8 and 15 (before dosing nab-paclitaxel and gemcitabine), and Day 22 to assess for events qualifying as dose limiting toxicities (DLTs). During Cycle 1, renal function (creatinine) must be checked on Days 8 and 15 before dosing nab-paclitaxel and gemcitabine. From Cycle 2 onwards, liver (AST, ALT, and bilirubin) and renal (creatinine) function tests must be performed only before dosing nab-paclitaxel and gemcitabine. For patients with Grade ≥3 AST/ALT, close clinical monitoring with an increased frequency of relevant blood testing should be undertaken, eg, every 2 - 3 days. The list of required laboratory tests is provided in Section 7.1.3, Laboratory Safety Assessments.
10. **Coagulation:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. The list of required laboratory tests is provided in Section 7.1.3 Laboratory Safety Assessments.
11. **Urinalysis:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. The list of required urine laboratory tests is provided in Section 7.1.3, Laboratory Safety Assessments.
12. **Pregnancy Test:** Pregnancy tests (serum/urine) for female patients of child bearing potential. Test may also be repeated as per request of Institutional Review Board/Independent Ethics Committee (IRB/IECs), if required by local regulations. FSH will be done at Screening only in females who are amenorrheic for at least 12 consecutive months. See Section 7.1.1 Pregnancy Testing for further details.
13. **Viral disease screening tests:** HBsAg, HbcAb, HCVAb, and HIV to be conducted by local laboratory where required by local regulations or if warranted by patient history.

14. **Triplicate 12-lead ECG:** At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected at the following timepoints: Screening, Cycle 1 Day 1 (pre-dose and 1 hr post-dose), Cycle 1 Day 3 (pre-dose, 1 and 4 hrs post-dose), Cycle 1 Day 22 (pre-dose, 1 and 4 hrs post-dose), Day 1 of Cycles 2 and 3 at pre-dose and 1 hr post-dose, and at the End of Treatment Visit.

    After Cycle 3, ECGs can be performed as clinically indicated. All ECG collection time points are with respect to PF-04136309 morning dosing. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTc is prolonged (value of >480 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation; further guidance is provided in the Section 7.1.6.

15. **Registration:** Patient identification number and dose level allocation to be operated by the Sponsor (see Section 5.1, Allocation to Treatment).

16. **PF-04136309 treatment:** Treatment will be administered in 28-day cycles. PF-04136309 will be administered twice daily on a continuous basis. Treatment will continue until PD, unacceptable toxicity or patient refusal, whichever occurs first. If PD occurs during treatment, continuation of one or more combination agents may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor. The patient will be reminded not to take their dose at home on clinic days (Cycle 1 days 1, 2, 3, 4, 8, 15, 16, and 22, and subsequent cycles days 1, 8, and 15), but to bring their bottle into clinic so that study drug may be administered after study visit assessments are completed, PK samples have been collected and nab-paclitaxel and gemcitabine have been administered prior to the PF-04136309 or placebo dosing. PF-04136309 or placebo should be taken approximately the same time each day, approximately 12 hours apart. The allowable treatment window for PF-04136309 or placebo is ±4 hours. PF-04136309 dosing should not be taken sooner than 8 hours and no more than 16 hours following the last PF-04136309 dosing.

17. **Nab-Paclitaxel treatment:** Treatment will be administered in 28-day cycles. Nab-paclitaxel will be administered first, on Days 1, 8 and 15 of each cycle followed by 1 week off treatment (Schedule 3/1). Treatment will continue until PD, unacceptable toxicity or patient refusal, whichever occurs first. If PD occurs during treatment, continuation of one or more combination agents may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor.

18. **Gemcitabine treatment:** Treatment will be administered in 28-day cycles. Gemcitabine will be administered immediately after nab-paclitaxel, on Days 1, 8 and 15 of each cycle followed by 1 week off treatment (Schedule 3/1). Treatment will continue until PD, unacceptable toxicity or patient refusal, whichever occurs first. If PD occurs during treatment, continuation of one or more combination agents may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor.

19. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. CT or MRI scans are to be performed every 8 weeks – efficacy assessments start at the end of Cycle 2 Day 28, prior to the start of Cycle 3. The allowable time window for disease assessments is ±7 days while on treatment and up to -7 days for screening (ie, the screening time window is up to 35 days prior to registration). Brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases. Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation. When the study treatment is discontinued for reasons other than disease progression or patient refusal, patients will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) patient refusal or (c) start of another anti-cancer treatment, whichever occurs first. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Responses of CR or PR must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met.

20. **Adverse Events:** Adverse Events (AEs) should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs according to Section 8.1. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
21. **Concomitant Medications:** Concomitant medications and treatments must be recorded on the CRF.
22. **Core Needle Biopsy (CNB):** Optional, paired collections (at least 12 paired sampled in each treatment arm of Phase 2) of Core Needle Biopsy from a site of major metastases will be performed at Screening and at Cycle 1 Day 28 (±7 days) or at Cycle 2 Day 28 (±7 days) , study day 56 only, if C1D28 sample not obtained. A Core Needle Biopsy sample collection from a a metastatic site will be performed unless it poses a safety risk to the patient, in the opinion of the Investigator and only after discussion with the Sponsor (refer to Section 7.3 for further guidance). An end of treatment CNB collection of a metastatic site may also be collected if agreement from patient, Investigator and Sponsor is obtained. Details for handling of these samples including processing, storage, and shipment will be provided in the central laboratory manual. A summary of planned analysis for CNB is provided in Section 9.5.2.
23. **Fine-Needle Aspirate (FNA):** Fine-needle aspirate will be collected only if a Core Needle Biopsy from a metastatic site is not viable. Optional paired collections will be performed at Screening and at Cycle 1 Day 28 (±7 days) or at Cycle 2 Day 28 (±7 days), study day 56 only, if C1D28 sample not obtained. An end of treatment FNA collection from the primary tumor may also be collected if agreement from patient, Investigator and Sponsor is obtained. Details for handling of these samples including processing, storage, and shipment will be provided in the central laboratory manual. A summary of planned analysis for FNA is provided in Section 9.5.2.
24. **Bone Marrow Aspirate:** An optional bone marrow aspirate will be performed at Screening and repeated at Cycle 1 Day 28 (±7 days) or at Cycle 2 Day 28 (±7 days), study day 56 only, if C1D28 sample not obtained.
25. **Blood for Biomarker Analyses – see Table 2 outlining activities.**
26. **Pharmacokinetics –** see Section 7.2 for Table outlining activities.
27. **Banked Biospecimens:** A 4 mL whole blood sample will be collected at the Screening Visit and Day 1 of Cycle 3 pre-dose (±3 days) to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to PF-04136309, or the identification of those patients who might preferentially benefit from treatment with PF-04136309 Patients will be asked to indicate on the consent form whether they will allow this sample to be also used for the Optional Pharmacogenomic Research as described in the Section 7.5.
28. **End of Treatment**: Obtain these assessments if not completed in the last week. Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation.

29. **Follow-up:** At least 28 days, and no more than 35 days after discontinuation of treatment, patients will return to undergo review of concomitant medications and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. When the study treatment is discontinued for reasons other than disease progression or patient refusal, patients will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) patient refusal or (c) start of another anti-cancer treatment, (whichever occurred first).
30. **Survival:** After treatment discontinuation, patient survival status will be collected every 3 months until death (telephone contact acceptable).
31. **EORTC QLQ-C30 in combination with QLQ-CIPN20:** Questionnaires will be completed prior to any study or medical procedure on Cycle 1 Day 1 (-2 day window), Day 1 of all subsequent cycles, and at the End of Treatment visit. One final questionnaire will be completed 4 weeks after discontinuation of IP during the Follow-up Visit. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. Interviewer administration in the clinic may be used under special circumstances (see Appendix 6 and Appendix 7).

PHARMACOKINETIC AND PHARMACODYNAMIC SAMPLING SCHEDULE

Table 2. Pharmacokinetic and Pharmacodynamic Sampling Schedule

	Screen (≤28 days)	Cycle 1 (28 days)								Subsequent Cycles (28 Days)			End of Treatment	Follow-up
Protocol Activity		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day 15**	**Day 16**	**Day 22**	**Day 1 (±3 days)**	**Day 8**	**Day 15**		
Allowable Visit Windows	**days**	**±1**	**±1**	**±1**	**±1**	**-1 day/ +3 days**	**-1 day/+ 3 days**	**±1**	**±3**	**±3**	**-1 day/+ 3 days**	**-1 day/ +3 days**	**±7**	**±7**
Pharmacokinetic Assessments														
PK of PF-04136309 (whole blood)[1]		X	X			X	X	X		X			X	
Target Engagement Biomarker														
Ex vivo CCL2-induced Phospho ERK (whole blood)[2]		X	X [pre-dose]	X [pre-dose]	X [pre-dose]									
Pharmacodynamic and Immunophenotyping Biomarkers														
Immune Cell Phenotyping (whole blood)[3]	X	X	X			X	X			X (Cycles 2, 3, 4, 7, 10)			X	
CCL2, Cytokines, Chemokines (whole blood)[5]	X	X	X			X	X			X (Cycles 2, 3, 4, 7, 10)			X	X
TBNK Absolute Counts (whole blood)		X				X	X			X		X	X	(X)
C Reactive Protein (hsCRP)		X				X	X			X		X	X	(X)
CCI [redacted]														
[redacted]														

Legend: (X) = Optional activity to be executed only if applicable. C = Cycle

Footnotes (Pharmacokinetic and Pharmacodynamic Sampling Schedule)

1. **Pharmacokinetic blood sampling:**

   Phase 1b Dose Escalation Cohorts: blood samples for determination of the PF-04136309 concentrations will be collected at the following timepoints:

   - Cycle 1 Day 1: within 6 hours prior to the first PF-04136309 dose on Cycle 1 Day 1;
   - Cycle 1 Day 2 and Day 8: within 30 minutes prior to the morning dose of PF-04136309;
   - Cycle 1 Day 15: 0 hour (within 30 minutes prior to the morning dose of PF-04136309), and 0.5, 1, 2, 3, 4, and 6 hours after the morning dose;

- Cycle 1 Day 16: within 30 minutes prior to the morning dose of PF-04136309;
- Day 1 of Cycle 2 and subsequent cycles: within 30 minutes prior to the morning dose of PF-04136309;
- End of Treatment visit.

Phase 2: blood samples for determination of the PF-04136309 concentrations will be collected at the following timepoints:

- Cycle 1 Day 1: within 6 hours prior to the first PF-04136309 dose on Cycle 1 Day 1;
- Cycle 1 Day 2, Day 8, Day 15: within 30 minutes prior to the morning dose of PF-04136309;
- Day 1 of Cycle 2 and subsequent cycles: within 30 minutes prior to the morning dose of PF-04136309;
- End of Treatment visit.

On days when patients have clinical visits where PK assessments are to be obtained, the morning dose of PF-04136309 should be held (NOT taken) prior to the study visit. On those days, the PF-04136309 morning dose can be taken after the study procedures required immediately prior to the morning dose have been performed.

A PK sample should be collected matched with a biomarker sample any time an unscheduled/optional biomarker sample or FNA or core needle biopsy [±2 hrs] is collected.

PK samples collected from patients randomized to receive nab-paclitaxel + gemcitabine + placebo (ARM B) will not be analyzed.

2. **Target Engagement:** A 3 mL whole blood sample will be collected on Cycle 1 Day 1 pre-dose, 2 and 6 hours post-dose, Day 1, 12 hour (pre-second BID dose-optional collection, ±4 hours dependent on last dose), Day 2, pre-dose (24 hour, ±4 hours dependent on last dose), Day 3, pre-dose (48 hour, ±4 hours dependent on last dose) and Day 4, pre-dose (72 hour, ±4 hours dependent on last dose). The ex vivo inhibition of CCL2-induced, ERK phosphorylation by PF-04136309 will be measured in whole blood using flow cytometry.
3. **Immune Cell Phenotyping**: A 10 mL whole blood sample will be collected at screening, Days 1 (pre-dose), Day 2, 8, and 15 of Cycle 1, Day 1 of Cycles 2, 3, 4, 7, 10, and at End of Treatment. An additional 6 mL whole blood sample will be collected at Cycle 1 Day 1 and Cycle 2 Day 1 (both pre-dose). Immune cell phenotypes and functionality associated with anti-tumor immunity and immune regulation (eg, CD14+/CCR2+ monocytes) will be measured by flow cytometry and/or immunoassays.
4. **RNA Profiling Peripheral Blood:** A 2-2.5 mL whole blood sample will be collected at Day 1 (pre-dose), Day 2, 8, and 15 of Cycle 1, Day 1 (pre-dose) of Cycles 2, 4, 7 and at End of Treatment. Will be collected to assess the expression profile of immune and tumor-related transcripts.
5. **Monitoring of CCL2 and immune regulatory cytokines**: A 4.5 mL whole blood sample will be collected at screening, Days 1 (pre-dose), Day 2, 8, 15, 22 of Cycle 1, Day 1 of Cycles 2, 3, 4, 7, 10, at End of Treatment and Follow-up to measure levels of the CCR2 Ligand, CCL2, and immunomodulatory cytokines.
6. **T Cell Repertoire in Peripheral Blood:** 4 mL whole blood sample will be collected at Screening, Day 1 (pre-dose), Day 8 and Day 15 of Cycle 1, Day 1 and Day 15 of Cycle 2, Day 1 of Cycles 4, 7, and End of Treatment. DNA may be isolated and be submitted to sequencing of T cell receptor genes.

1. INTRODUCTION

Progress in basic and translational immunology has confirmed the importance of the immune system in cancer progression and in its treatment and has renewed interest in immune-based therapy for cancer, including pancreatic cancer. The main cellular components contributing to the immunosuppressive microenvironment include myeloid-derived suppressor cells (MDSC), tumor associated macrophages (TAM), mast cells, and T regulatory cells (Treg).[1,2] Of these, MDSC comprise a heterogeneous population of the immature cells arising from the myeloid lineage, and they are considered to be the key in orchestrating the suppressive tumor microenvironment. Myeloid-derived suppressor cells are increased in many pathological conditions such as infections, inflammatory disease, sepsis, traumatic shock, and pancreatic cancer.[3,4] Myeloid-derived suppressor cells are observed with increased prevalence in the peripheral blood and in the tumor microenvironment of patients with solid tumors, including pancreatic cancer.[5] Moreover, the number of circulating MDSC significantly correlates with clinical state and metastatic tumor burden[6], and elimination of MDSC has been shown to improve antitumor activity.[7,8,9,10] Because MDSC are proven to be one of the main mechanisms of tumor evasion from the immune system, the pharmacological modulation of MDSC and prevention of their appearance or infiltration to solid tumors represent potential novel and innovative therapeutic strategies in cancer.[9,11,12,13,14,15,16]

While the mechanisms responsible for MDSC expansion and trafficking to tumors is not entirely understood, it has been shown that MDSCs express CCR2 and that the CCL2/CCR2 signaling axis contributes to tumor progression through the CCR2 mediated MDSC recruitment and/or accumulation.[17,18,19]

1.1. Mechanism of Action/Indication

PF-04136309 is an orally active CCR2 antagonist. It is selective for CCR2 against a panel of human chemokine receptors. When evaluated against human monocytes and human whole blood, PF-04136309 blocked CCR2 mediated signal transduction, chemotaxis and CCL2 binding at similar concentrations. While initially developed for the treatment of acute and chronic pain and liver fibrosis, the focus of development is now on oncological indications.

1.2. Background and Rationale

1.2.1. Study Rationale

Not only do MDSCs express the chemokine receptor CCR2, but in murine models of pancreatic cancer, it has been shown that MDSCs are upregulated in the tumor bearing host, promote tumor growth, suppress antitumor immunity and when depleted result in increased survival.[5] Additionally it has been shown that CCR2 is upregulated on MDSC in both the circulation and tumor and that PF-04136309 can effectively block MDSC recruitment resulting in significantly reduced tumor growth.

Based on these findings it is hypothesized that CCR2 may be a promising therapeutic target in pancreatic cancer, a tumor associated with a marked up regulation of MDSCs in the tumor microenvironment in both mouse models and human patients.

Beside the potential interest in terms of anti-tumor efficacy, the expression of CCL2 and CCR2 is upregulated by dorsal root ganglia neurons in rodent models of neuropathic pain. CCL2 increases the excitability of nociceptive neurons after a peripheral nerve injury, and disruption of CCL2 signaling blocks the development of neuropathic pain.[20] Furthermore, several authors reported that induction of CCL2 and its receptor CCR2 in primary sensory neurons contributes to paclitaxel-induced peripheral neuropathy (CIPN).[21,22] Activation of paracrine CCL2/CCR2 signaling between dorsal root ganglion neurons plays a critical role in the development of paclitaxel-induced peripheral neuropathy. Preclinically, paclitaxel induces increased expression of CCL2 in spinal astrocytes. Local blockade of CCL2/CCR2 signaling by anti-CCL2 antibody or CCR2 antisense oligodeoxynucleotides significantly attenuates paclitaxel CIPN phenotypes including mechanical hypersensitivity and loss of intraepidermal nerve fibers in hindpaw glabrous. Targeting CCL2/CCR2 signaling could be a novel therapeutic approach.[22] A potential beneficial effect of PF-04136309 on paclitaxel-CIPN will be assessed through EORTC CIPN20 questionnaire[23,24,25,26,27] and NCI-CTC AE.[25,26,27,28]

Complete information for PF-04136309 may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.

The SRSD for Gemcitabine (Gemzar®) is the Eli Lilly UK Summary of Product Characteristics (SmPC).

The SRSD for nab-paclitaxel (Abraxane®) is the US Package Insert (USPI).

1.2.2. Dose Rationale

PF-04136309 was studied in healthy subjects after a single oral dose over the dose range of 1 to 1000 mg, and after repeated oral administration at 5 to 500 mg twice daily (BID) for 14 consecutive days. These doses were generally safe and well tolerated with no dose limiting adverse events. Using phosphorylation of ERK (pERK) as a whole blood biomarker for the pharmacologic inhibition of CCR2 inhibition, these studies showed that PF-04136309 maximally suppressed pERK phosphorylation in whole blood monocytes for at least 12 hours at doses ≥150 mg, which suggest a complete or near complete saturation of circulating CCR2 at doses ≥150 mg twice per day (BID).

PF-04136309 at a dose of 500 mg BID has been combined with FOLFIRINOX (fluorouracil, leucovorin calcium, irinotecan hydrochloride, and oxaliplatin) chemotherapy in a Phase 1/2 study (NCT01413022)[39] in 39 patients with borderline and locally advanced pancreatic cancer. The study design did include 6 patients treated with FOLFIRINOX alone. Comparison of toxicities between the 2 groups of patients showed that the combination of PF-04136309 and chemotherapy (cohort B + expansion phase) was well tolerated with most of the observed adverse events being attributed to the chemotherapy. The most commonly reported treatment-related haematological adverse events (AEs) in the cohort B + expansion phase (N=39) included neutropenia n=28 (21.8%) all grade and n=26 (66.7%) ≥Grade 3. The most commonly reported treatment-related non-hematological AEs in the cohort B + expansion phase included: fatigue n=26 (66.7%) all grade and n=1 (2.6%) ≥Grade 3. Also, it

was observed that PF-04136309 at 500 mg BID inhibited the migration of inflammatory monocytes from the bone marrow to the tumor, and depleted tumor infiltrating regulatory T-cells.

While the mechanisms responsible for MDSCs expansion and trafficking to tumors are not entirely understood, it has been shown that MDSCs express CCR2 and that the CCL2/CCR2 signaling axis contributes to tumor progression through the CCR2-mediated MDSC recruitment and/or accumulation. No data is available regarding the exposure-response relationship of PF-04136309 for CCR2 occupancy on MDSCs in the tumor.

Previous non-oncology and oncology studies have shown that repeated administration of PF-04136309 at 500 mg BID appears to be safe and pharmacologically active. Doses higher than 500 mg, ie, 750 mg and 1000 mg have been evaluated as single dose but not following repeated administration. In the phase 1 escalation phases, no DLTs have been reported and toxicities were mild.

Given the uncertainty whether the PF-04136309 exposure achieved after 500 mg BID dosing would be able to maximally occupy CCR2 in the tumor, the dose finding in the present study will start with the PF-04136309 dose of 750 mg BID, to be given in combination with nab-paclitaxel and gemcitabine. The dose of 1000 mg BID is considered as the maximal feasible dose for the study. Strict de-escalation rules will apply and lower dose levels may be explored.

Nab-paclitaxel and gemcitabine will be administered according to the approved dosing schema in this indication.

1.2.3. Biomarker Rationale

The objective of biomarker collections and analyses is to provide evidence of target engagement (TE) pharmacodynamic activity and proof of mechanism (POM) of PF-04136309 in combination with nab-paclitaxel + gemcitabine. This will provide data to characterize the relationship between PF-04136309 TE, pharmacodynamic activity, and any observed disease modifying effects. Furthermore, this may enable the identification of patients and/or tumor phenotypes most likely to respond to PF-04136309, nab-paclitaxel + gemcitabine combination therapy.

Target engagement will be assessed using a flow cytometry assay to measure the inhibition of ERK kinase phosphorylation in whole blood samples exposed to the CCR2 ligand, CCL2, ex vivo. If sufficient data is collected to characterize TE at the RP2D in Phase 1b, this assessment will not be included in Phase 2 of the study. Tumor-associated macrophages (TAMs) have been shown to support both primary tumor survival and eventual metastases by inhibiting anti-tumor immunity, establishing a toleragenic microenvironment and seeding sites of metastases.[20,30,31] Tumor-associated macrophages are derived from CD14+CCR2+ inflammatory monocytes (IMs) which leave the bone marrow and traffic to the tumor and sites of metastases in response to production of the CCR2 ligand, CCL2.[32] Once resident in this tissue, these monocytes convert to a TAM phenotype which inhibits anti-tumor T cell activity and promote the shift to a toleragenic tumor microenvironment.[33,34] Inhibition of

CCR2 activity by PF-0413609 has been shown in pre-clinical and clinical studies to increase the ratio of IMs in the bone marrow to that in the peripheral blood, deplete TAMs from primary tumors and inhibit metastases to lung and liver. Evidence for this mechanism being active during PF-04136309, nab-paclitaxel + gemcitabine combination therapy will be provided by measurement of IM and TAM in the peripheral blood, bone marrow aspirates and fine-needle aspirates (FNAs) or core needle biopsy of metastases and/or primary tumor by flow cytometry.

Accumulation of the CCR2 ligand, CCL2, has been associated with a rebound of metastases after cessation of antibody-mediated blockade of CCR2 in pre-clinical breast cancer models.[38] Plasma samples will be collected and assayed for CCL2, cytokines and chemokines by immunoassay to monitor for CCL2 accumulation and potential effects on components of adaptive immunity.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Phase 1b Dose Finding Objectives

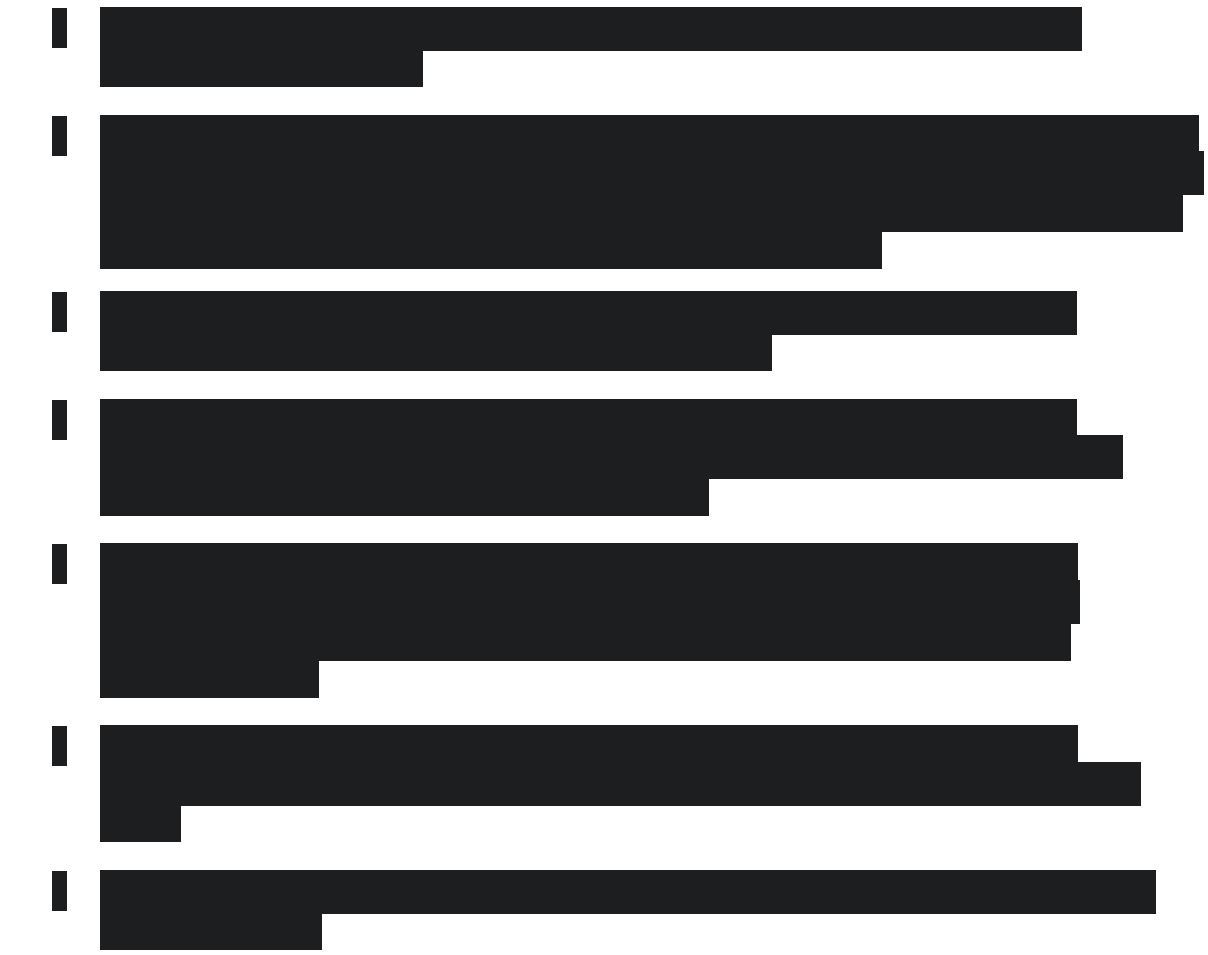
Primary Objectives

- To evaluate the safety and tolerability of PF-04136309 in combination with nab-paclitaxel + gemcitabine in patients with metastatic pancreatic ductal carcinoma.
- To characterize the Dose Limiting Toxicities (DLTs) and overall safety profile of escalated doses of PF-04136309 and the associated schedule.
- To determine the maximum tolerated dose of PF-04136309 and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives

- To evaluate the pharmacokinetics (PK) of PF-04136309 when given in combination with nab-paclitaxel + gemcitabine in combination.
- To characterize the ex vivo inhibition of CCL2-induced ERK kinase phosphorylation as a measure of target engagement following treatment with PF-04136309 in combination with nab-paclitaxel + gemcitabine at each dose level.

CCI



2.1.2. Phase 2 Randomized Double Blinded Placebo Controlled Study

Primary Objective

- To assess the enhancement of efficacy of PF-04136309 in combination with nab-paclitaxel + gemcitabine versus nab-paclitaxel + gemcitabine + placebo in terms of PFS.

Secondary Objectives

- To assess the enhancement of efficacy of PF-04136309 in combination with nab-paclitaxel + gemcitabine versus nab-paclitaxel + gemcitabine + placebo in terms of OS.
- To assess the enhancement of efficacy of PF-04136309 in combination with nab-paclitaxel + gemcitabine versus nab-paclitaxel + gemcitabine + placebo in terms of ORR and duration of response.
- To evaluate the safety and tolerability of PF-04136309 in combination with nab-paclitaxel + gemcitabine.
- To evaluate the population PK of PF-04136309 given in combination with nab-paclitaxel + gemcitabine.
- To validate the proof of mechanism of PF-04136309 in combination with nab-paclitaxel + gemcitabine compared to nab-paclitaxel + gemcitabine + placebo.
- To evaluate to evaluate the improvement of peripheral neurotoxicity induced by nab-paclitaxel by the addition of PF-04136309 to the combination therapy of nab-paclitaxel + gemcitabine.

CCI

[redacted]

- To explore the effects of PF-04136309 in combination with nab-paclitaxel + gemcitabine on the prevalence and diversity of tumor antigenic epitopes in tumor tissue.

- To correlate the levels of tumor markers, including but not limited to CA19.9 with clinical response.

2.2. Endpoints

2.2.1. Phase 1b Dose Finding Endpoints

Primary Endpoint

- Dose Limiting Toxicities (DLTs) in order to determine the MTD and RP2D.

  Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) timing, seriousness and relationship to study therapy.

- Lab abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 4.03) and timing.

Secondary Endpoints

- PK parameters of PF-04136309 after multiple dosing, including $C_{max,ss}$, T_{max}, $AUC_{tau,ss}$, $C_{min,ss}$, CLss/F, and as data permit, $t_{1/2}$ and Vss/F.

- Ex vivo inhibition of CCL2-induced ERK kinase phosphorylation in the peripheral blood.

CCI

[redacted]

2.2.2. Phase 2 Randomized Double Blinded Placebo Controlled Study Endpoints

Primary Endpoint

- Progression Free Survival (PFS).

Secondary Endpoints

- Overall Survival (OS).
- Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study treatment.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.
- Objective response rate (ORR).
- Duration of Response. [The rate of progression-free survival at 1 year, the rate of disease control (confirmed response or stable disease for ≥16 weeks)].
- Time to progression with the double combination PF-04136309 and gemcitabine (maintenance therapy) after interruption of nab-paclitaxel.
- Trough PF-04136309 concentrations.
- PD markers in metastatic tumors and bone marrow: Pre-biopsy – Post-biopsy after 1 or 2 cycles of PF-04136309 + nab-paclitaxel + gemcitabine or nab-paclitaxel + gemcitabine + placebo.
- Peripheral neurological adverse events as characterized by frequency, severity (as graded by NCI CTCAE v.4.03 and by self-assessment according to the EORTC QLQ-CIPN20 questionnaire), and timing.

CCI [redacted]

- Presence or levels of expression of several tumor biomarkers and their relationship to clinical responsiveness (including but not limited to tumor markers, CA 19.9).

3. STUDY DESIGN

3.1. Study Overview

This is a multi-center Phase 1b/2 study in the first line treatment of patients with mPDA.

The Phase 1b will be open label as patients will receive ascending doses of PF-04136309 in combination with nab-paclitaxel + gemcitabine. The Phase 2 will be controlled, randomized and double blinded as patients will be randomized to receive PF-04136309 in combination with nab-paclitaxel + gemcitabine (ARM A) versus nab-paclitaxel + gemcitabine + placebo (ARM B: Standard of Care).

-Phase 1b study: Open label dose finding.

In the dose finding phase, patients will be enrolled in cohorts of 2 to 4 patients, starting with 750 mg BID of PF-04136309 for the first cohort. A new cohort of n=2 to 4 patients exposed to the same dose 750 mg BID could be opened after safety has been established for at least the first cycle in all patients in the previous cohort. A higher dose level at 1000 mg BID may also be explored.

If at the dose level of 750 mg BID, more than 33% (ie, >1/3, >2/6) of the patients experiences a DLT related to PF-04136309 (see Section 3.3 and 9.2.2), a lower dose level of 500 mg BID may be evaluated.

The dose escalation in this stage may not be able to identify a MTD, as DLTs may not be frequently observed after administration of this investigational agent. Based on safety and other results (eg, PK) from patients enrolled in the dose escalation cohorts, a dose level will be selected to be further evaluated as the Recommended Phase 2 Dose (RP2D). A minimum of 6 patients, up to 12 patients, will be treated at this dose level to establish it as the RP2D.

-Phase 2 study: Randomized double blinded placebo control.

Approximately 92 patients will be randomized with a 1:1 to receive PF-04136309 in combination with nab-paclitaxel + gemcitabine (ARM A; n=46) versus nab-paclitaxel + gemcitabine + placebo (ARM B; n=46). Randomization will be stratified by site (two strata: the site of University of Rochester, and other sites).

The primary objective will be the enhancement of efficacy in terms of PFS (see Section 9.4.1).

In both studies, treatment may continue until progression of disease (PD) unacceptable toxicity or patient refusal, whichever comes first. After 6 months, in case of neurological or hematological chronic ≥ Grade 2 toxicity, nab-paclitaxel may be stopped and gemcitabine + PF-04136309 will be continued until disease progression or patient's or investigator's decision. If gemcitabine is not well tolerated, treatment may be continued with PF-04136309 alone until disease progression or patient's or investigator's decision.

The proof of mechanism of action of PF-04136309 will be assessed by the comparison of at least 12 paired (optional) biopsies from each treatment arm, bone marrow aspirates and peripheral blood (pre- and post- treatment in the Phase 1b and Phase 2 study). Their optional collection will provide baseline, pre-dose core needle biopsy (CNB) from a metastatic site, or fine-needle aspirate (FNA) from the primary tumor tissue, if a sample from the metastatic site is not viable, and/or bone marrow aspirates. Paired CNB, or FNA, and/or bone marrow aspirates will be collected following the completion of Cycle 1 at C1D28 [±7 days] or at C2D28 [±7 days] if the collection at Cycle 1 is not obtained.

Serial blood samples will be collected from patients enrolled in the Phase 1b cohorts to determine the multiple dose PK of PF-04136309 given in combination with nab-paclitaxel + gemcitabine. Sparse PK sampling will be performed for patients enrolled in the Phase 2 portion of the study to evaluate the population PK of PF-04136309.

One of the key elements of this study is the possibility to evaluate potential molecular targets that could be modified in vivo by the drug combination used in this study. In the combination setting, this is especially important for PF-04136309 and nab-paclitaxel + gemcitabine, as their MTDs as single agents may exceed the MTD required to induce a maximal effect in combination.

The biomarker studies will be used to help understand the in vivo mechanism of action of the agents studied as well as potential mechanisms of resistance. The studies may help in the future development of PF-04136309 as a single agent, or in combination with other compounds.

3.2. Dose Finding and Stopping Rules (Phase 1b)

A modified toxicity probability interval method (mTPI) targeting a DLT rate of 27.5% with an equivalence interval (22.5%-32.5%) will be utilized in order to estimate MTD. Patients will be enrolled in cohorts of 2-4, starting with 750 mg BID of PF-04136309 for the first cohort. A higher dose at 1000 mg BID may be explored after evaluation of the Cycle 1 safety and other results from patients enrolled at 750 mg BID. Escalation to a higher dose (eg 1000 mg BID) will require that at least 6 patients are dosed at 750 mg BID and no more than 1 experienced a DLT. If more than 33% of the patients (ie, >1/3, >2/6) at the dose level of 750 mg BID experience a DLT related to PF-04136309, a lower dose level at 500 mg BID will be evaluated.

After evaluating the safety and other results (eg, PK) from patients enrolled in the dose escalation cohorts, a dose level will be selected to be further evaluated as the Recommended Phase 2 Dose (RP2D). A minimum of 6 patients, up to 12 patients, will be treated at this dose level to establish it as the RP2D. To further evaluate safety and pharmacodynamics, the number of patients enrolled during this part of the study (Phase 1b) may be N up to 20. The study will stop if all PF-04136309 doses explored appear to be overly toxic.

3.3. Dose Limiting Toxicity (DLT)

DLTs will be defined as any of the following events described below that occur in the first cycle of treatment (Day 1 through 28) and are attributed (ie, judged to be at least possibly related) to the combination of PF-04136309 with nab-paclitaxel and gemcitabine where relationship with the combination cannot be ruled out. DLTs will be classified according to CTCAE version 4.03.

Hematologic:

- Grade 4 neutropenia lasting >5 days;
- Febrile neutropenia [defined as absolute neutrophils count (ANC) <1,000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour];
- Grade ≥3 neutropenic infection;
- Grade ≥3 thrombocytopenia with Grade ≥2 bleeding;
- Grade 4 thrombocytopenia.

Non-Hematologic:

- Grade 3 toxicities, except:
    - Nausea and vomiting responding to prophylaxis and/or treatment and lasting less than 7 days from each chemotherapy infusion period;
    - Diarrhea responding to treatment and lasting less than 7 days;
    - Grade 3 Fatigue lasting less than 7 days;
    - Grade 3 QTc prolongation (QTc >500 msec) will be considered a DLT only if persisting after correction of any reversible causes. So, Grade 3 QTc prolongation will first require repeat testing, re-evaluation by a qualified person, and correction of reversible causes such as electrolyte abnormalities or hypoxia for confirmation;
    - Grade 3 aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) increase lasting ≤7 days.
- All Grade 4 toxicities;
- Delay of more than 2 weeks (14 calendar days) in receiving the next scheduled cycle due to persisting treatment-related toxicities.

A subject is classified as DLT-evaluable if he/she experiences a DLT or if he/she otherwise in the absence of a DLT receives at least 85% of the planned doses of each study drug in the first 28 day cycle. If a subject is withdrawn from study for any reason other than a DLT prior to completion of the 28-day safety observation period, a replacement subject will be assigned the same dose as the replaced subject.

Adverse Effects of Interest are defined as those adverse events that fulfill the same grade and terms that would qualify as a DLT but occur beyond the protocol defined 28-day DLT window. Any Adverse Event of Interest that occurs should be reported to Pfizer as they occur and entered into the electronic case report form (eCRF).

3.4. Late Onset Toxicity and Toxicities

Adverse events that meet the same grading criteria as the DLT criteria listed above occurring after the DLT observation period will lead Pfizer to immediately schedule a meeting with the investigators to review the details of the potential late onset toxicity and determine if the enrollment has to be held for this dose level or if a dose reduction should be implemented for all ongoing patients. Late onset toxicities meeting the definition of a DLT will be used in the evaluation of the MTD.

3.5. Maximum Tolerated Dose/Recommended Phase 2 Dose

These 2 concepts may be determined after a full evaluation of safety and efficacy data from patients treated in the escalation phase of the study.

3.6. Recommended Dose Modifications

Every effort should be made to administer study treatment on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in 3 ways:

Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, of study drugs during a given treatment cycle.

Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.

In the next cycle: dose reduction may be required in a subsequent cycle based on worst toxicity experienced in the previous cycle.

3.7. Dose Interruptions/Delays/Reductions

3.7.1. PF-04136309-Induced Dose Interruptions and Delays

PF-04136309 does not have to be interrupted in case of hematologic toxicity or peripheral neurotoxicity with the exception for Grade 4 hematological toxicity (see Table 3. Recommended Dose Modifications for Neutropenia and/or Thrombocytopenia). PF-04136309 should be interrupted in case of > Grade 2 non-hematologic or non-peripheral neurological toxicity, potentially due to PF-04136309.

3.7.2. Chemotherapy-Induced Dose Interruptions and Delays

A new chemotherapy cycle (both agents) may not start (Cycle Day 1) until the following parameters have been met:

- ANC ≥1,500/µL;
- Platelets count ≥100,000/µL;
- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the Investigator discretion, Grade ≤2, if not considered a safety risk for the patient).

PF-04136309 and gemcitabine cannot be administered until the following parameters have been met:

- AST and ALT ≤2.5 x ULN; ≤5.0 x ULN if liver involvement by the tumor.

In addition, gemcitabine cannot be administered until:

- Creatinine ≤1.0 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If starting of the next cycle is delayed for toxicities attributable only to nab-paclitaxel and/or gemcitabine, the administration of PF-04136309 may continue until the next administration of chemotherapy.

Nab-paclitaxel may be administered if hematological toxicities are recovered to the criteria reported above. See Table 4. Recommended Dose Modifications for Non Hematological Toxicities for guidelines on liver and renal function tests.

Gemcitabine administration must be omitted until liver and renal function tests return to the above reported value. If liver and renal toxicities persist beyond 14 days, gemcitabine as well as nab-paclitaxel and PF-04136309 should be interrupted.

If a treatment interruption continues beyond Day 28 of the current cycle, then the day when nab-paclitaxel and/or gemcitabine are restarted will be counted as Day 1 of the next cycle.

Overall, if toxicities (hematologic and non-hematologic) do not revert to acceptable levels as defined above, chemotherapy resumption must be delayed. The 14 days of treatment delay does not include the one week of no treatment in each 3/1 cycle of chemotherapy. A treatment delay or interruption of more than 14 days due to lack of recovery will result in discontinuation of the patient from treatment unless discussed and agreed with the sponsor.

Treatment resumption for patients recovering from treatment-related toxicities after 14 days can be considered only if there is a reasonable evidence of clinical benefit from one or more compounds, the safety of continuing one or more compounds is adequate, and after discussion with the Sponsor (including a discussion of which treatment will continue).

3.7.3. Dose Reductions

PF-04136309, nab-paclitaxel or gemcitabine doses may need to be reduced when treatment is resumed following dose interruption or cycle delay due to toxicity.

Table 5. Available Doses lists available doses for dose modifications of each drug.

No specific dose reductions are recommended for Grade 1 and 2 treatment-related toxicities, with the exception of some drug-related, non-hematological toxicities that are Grade ≥2, as reported in Table 4. However, Investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Dose reductions from the starting dose of 1 or 2 doses will be allowed, depending on the type and severity of toxicity encountered. Patients requiring dose reductions to exposure levels of PF-04136309 <250 mg, nab-paclitaxel <75 mg/m^2, gemcitabine <600 mg/m^2 will be discontinued from the treatment and entered into the follow up phase, unless otherwise agreed between the Investigator and the Sponsor.

All dose modifications/adjustments must be clearly documented in the patient's source notes and CRF.

Recommended dose reductions for neutropenia and/or thrombocytopenia at the start of a cycle or within a cycle are illustrated in Table 3.

Table 3. Recommended Dose Modifications for Neutropenia and/or Thrombocytopenia

Cycle Day	ANC (cells/mm^3)		PLT (cells/mm^3)	Action on Nab-Paclitaxel Dosing*	Action on Gemcitabine Dosing*	Action on PF-04136309 Dosing
Day 1	≥ 1500	AND	≥ 100,000	Treat as planned	Treat as planned	Treat as planned
	<1500	OR	<100,000	Delay dose by 1 week until recovery; if recovery is not observed in 1 week, delay by one additional week. If recovery is not observed after 2 weeks of delay, discontinue or discuss with Sponsor	Delay dose by 1 week until recovery; if recovery is not observed in 1 week, delay by one additional week. If recovery is not observed after 2 weeks of delay, discontinue or discuss with Sponsor	No change
Day 8	≥1000	AND	≥75,000	Resume full dose	Resume full dose	No change
	500 to <1000	OR	50,000 to <75,000	No delay, ↓ 1 dose level	No delay, ↓ 1 dose level	No change
	<500	OR	<50,000	Hold dose	Hold dose	Withhold until recovery
Day 15: If Day 8 chemotherapy was administered (any dose)						
	≥1000	AND	≥75,000	Resume full dose, even if the Day 8 dose was reduced	Resume full dose, even if the Day 8 dose was reduced	No change
	500 to <1000	OR	50,000 to <75,000	No delay; if the Day 8 dose was reduced, give same dose as Day 8; if Day 8 dose was not reduced, ↓ 1 dose level;	No delay; if the Day 8 dose was reduced, give same dose as Day 8; if Day 8 dose was not reduced, ↓ 1 dose level; G-CSF permitted based on Investigator judgment	No change
	<500	OR	<50,000	Hold dose; G-CSF permitted based on Investigator judgment	Hold doses; G-CSF permitted based on Investigator judgment	Withhold until recovery

Table 3. Recommended Dose Modifications for Neutropenia and/or Thrombocytopenia

Cycle Day	ANC (cells/mm^3)		PLT (cells/mm^3)	Action on Nab-Paclitaxel Dosing*	Action on Gemcitabine Dosing*	Action on PF-04136309 Dosing
Day 15: If Day 8 chemotherapy was withheld						
	>1000	OR	≥75,000	No delay; ↓ 1 dose levels from Day 1;	No delay; ↓ 2 dose levels from Day 1; G-CSF permitted based on Investigator judgment	No change
	500 to <1000	OR	50,000 to <75,000	No delay; ↓ 2 dose levels from Day 1;	No delay; ↓ 2 dose levels from Day 1; G-CSF permitted based on Investigator judgment	No change
	<500	OR	<50,000	Hold dose; G-CSF permitted based on Investigator judgment	Hold dose; G-CSF permitted based on Investigator judgment	Withhold until recovery

Abbreviations: ANC = Absolute Neutrophil Count; G-CSF = granulocyte-colony stimulating factors ; PLT= Platelet

Primary prophylactic use of granulocyte-colony stimulating factor (G-CSF) is not permitted until following completion of Cycle 2.

Recommended dose reductions for non-hematological toxicities at the start of a cycle or within a cycle are illustrated in Table 4.

Table 4. Recommended Dose Modifications for Non Hematological Toxicities

Toxicity (NCI CTCAE version 4.0)	Nab-Paclitaxel	Gemcitabine	PF-04136309
Infections			
Febrile Neutropenia Grade ≥3	Withhold until fever resolves and ANC ≥1500; then resume at next lower dose level	Withhold until fever resolves and ANC≥1500; then resume at next lower dose level	Withhold until recovery
Sepsis Grade 4 (with or without neutropenia)	Withhold until resolution of sepsis and ANC ≥1500; then resume at next lower dose level or discontinue as per Investigator judgment.	Withhold until resolution of sepsis and ANC ≥1500); then resume at next lower dose level or discontinue as per Investigator judgment.	Withhold until recovery
Nervous System Disorders			
Peripheral Neuropathy Grade ≥ 2	Withhold until ≤ Grade 1; then resume at next lower dose level or discontinue as per Investigator judgment.	Continue treatment. No dose reduction.	No change

Table 4. Recommended Dose Modifications for Non Hematological Toxicities

Toxicity (NCI CTCAE version 4.0)	Nab-Paclitaxel	Gemcitabine	PF-04136309
Skin & Subcutaneous Tissue Disorders			
Grade 2	Withhold until ≤ Grade 1; then resume at next lower dose level;	Withhold until Grade ≤1; then resume at next lower dose level;	Withhold until Grade ≤1 then resume at the same dose level; if toxicity recurs Grade ≥2 withhold until Grade ≤1 then resume at the same dose level or next lower dose level per Investigator's judgment.
Grade 3	Withhold until Grade ≤1 then resume at the next lower dose level.	Withhold until Grade ≤1 then resume at the next lower dose level.	Withhold until Grade ≤1 then resume at the next lower dose level.
Grade 4	Discontinue	Discontinue	Discontinue
Lung Disorders			
Interstitial Pneumonitis Grade ≥2	Discontinue after ruling out infectious etiology	Discontinue after ruling out infectious etiology	Withhold until recovery
Pulmonary Embolism Grade >2[(a)]	Withhold until recovery; then resume at next lower dose level or discontinue as per Investigator judgment	Discontinue	Withhold until recovery; then resume at next lower dose level or discontinue as per Investigator judgment
Gastrointestinal Disorders			
Stomatitis Grade 3	Withhold until ≤ Grade 1; then resume at next lower dose level	Withhold until ≤ Grade 1; then resume at next lower dose level	Withhold until recovery
Stomatitis Grade 4	Discontinue	Discontinue	Withhold until recovery
Diarrhea Grade 3 (despite maximal medical therapy)	Withhold until ≤ Grade 1; then resume at next lower dose level	Withhold until ≤ Grade 1; then resume at next lower dose level	Withhold until Grade ≤1; then resume at next lower dose level
Diarrhea Grade 4 (despite maximal medical therapy)	Discontinue	Discontinue	Discontinue
Nausea or Vomiting Grade ≥3 (despite maximal medical therapy and lasting more than 7 days)	Withhold until ≤ Grade 1; then resume at next lower dose level	Withhold until ≤ Grade 1; then resume at next lower dose level	Withhold until ≤ Grade 1; then resume at next lower dose level
Metabolic Disorders			
Hypophosphatemia Grade ≥3 (despite maximal replacement therapy)	No change	No change	No change
Immune System Disorders			
Hypersensitivity reactions Grade ≥3 [(b)]	Discontinue	Discontinue	Discontinue

Table 4. Recommended Dose Modifications for Non Hematological Toxicities

Toxicity (NCI CTCAE version 4.0)	Nab-Paclitaxel	Gemcitabine	PF-04136309
Renal and Urinary Disorders[c]			
Creatinine >1.0 x ULN or estimated creatinine clearance <60 mL/min as calculated	No change	Delay dose by 1 week until recovery, then resume at the next lower dose level; If no recovery by 2 weeks, discontinue	No change
Creatinine increase Grade ≥3	Withhold until ≤ Grade 1; then resume to next lower dose level	Discontinue	Withhold until ≤Grade 1; then resume to next lower dose level
Hepatic Disorders[d]			
AST and/or ALT >2.5 - 10 x ULN if no liver involvement; >5.0 - 10 x ULN if liver involvement	No change	Delay dose by 1 week until recovery to ≤ Grade 1 or baseline (ie, ≤2.5 or ≤5.0 x ULN if liver involvement by the tumor), then resume at the next lower dose level. If no recovery by 2 weeks, discontinue.	No change – Investigator may discuss with the Sponsor the need to withhold until recovery
AST and ALT >10 x ULN	Withhold until Grade ≤1 or baseline, then resume at next lower dose level or discontinuation	Discontinue	Withhold until ≤ Grade 1 or baseline, then resume at next lower dose level or discontinuation per Investigator's judgment.
Other Non-Hematological Toxicities			
Grade ≥3	Withhold until ≤ Grade 1; then resume at next lower dose level	Withhold until ≤ Grade 1; then resume at next lower dose level	Withhold until ≤ Grade 1; then resume at next lower dose level

Abbreviations: ANC = Absolute Neutrophil Count; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; ULN = upper limit of normal

(a). If a patient develops pulmonary embolism, only low-molecular weight heparin may be used for treatment. Oral anticoagulants and oral anti-thrombins are excluded from use.
(b). Severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy.
(c). Gemcitabine must be used with caution in patients with renal impairment. Cases of hemolytic uremic syndrome and/or renal failure (some fatal) have occurred with gemcitabine treatment.
(d). In the case of moderate to severe hepatic impairment, before implementing any dose modification, disease progression in the liver should be excluded.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriately qualified member of the Investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Histologically or cytologically-proven diagnosis of metastatic ductal adenocarcinoma of the pancreas.

2. All patients must provide a baseline tumor sample at registration. This can be an archival sample if collected within 1 year of study enrollment. If an archival sample is not available, patients must have a metastatic biopsy collected at the screening visit.

3. Patient must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of pancreatic metastatic disease. Prior treatment with Fluorouracil (5-FU) or 5-FU prodrug or gemcitabine administered as a radiation sensitizer or immune therapy at the exception of modulators of monocyte or TAM function in the adjuvant setting is allowed (with or without continued post radiation gemcitabine treatment as adjuvant chemotherapy), provided at least 3 months have elapsed since completion of the last dose and no lingering toxicities are present. Patients having received cytotoxic doses of any other chemotherapy in the pancreatic adjuvant setting are not eligible for this study.

4. Measurable disease as per RECIST v. 1.1.

5. Life expectancy ≥12 weeks.

6. Patients with clinically significant ascites may enter.

7. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 NCI CTCAE except for AEs not constituting a safety risk by Investigator judgment.

8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

9. Age ≥18 years.

10. Adequate Bone Marrow Function, including:

    - Absolute Neutrophil Count ≥1,500/μL or ≥1.5 x 10^9/L;

    - Platelets ≥100,000/μL or ≥100 x 10^9/L; Hemoglobin ≥9 g/dL.

11. Adequate Renal Function, including:

    - Serum creatinine ≤1.0 x upper limit of normal (ULN) or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

12. Adequate Liver Function, including:

    - Total serum bilirubin ≤1.0 x ULN unless the patient has documented Gilbert's syndrome;

    - Aspartate and Alanine Aminotransferase (AST and ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor.

13. Acceptable coagulation parameters as demonstrated by prothrombin time (PT) and partial thromboplastin time (PTT) within ±15% normal limits.

14. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.

15. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective method(s) of contraception throughout the study and for at least 28 days after the last dose of PF-04136309 and for 6 months after last dose of nab-paclitaxel, gemcitabine, or both.

16. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study.

17. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Patients with known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

2. Prior therapy with modulators of monocyte or TAM function.

3. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks of registering for the current study and/or during study participation.

4. Any surgery (not including minor procedures such as placement of port-a-caths) within 4 weeks of registering for the current study.

5. Diagnosis of any second malignancy within the last 3 years, except for adequately treated basal cell carcinoma, or squamous cell skin carcinoma or in-situ cervical carcinoma.

6. Known hypersensitivity to nab-paclitaxel or to any of the excipients.

7. Known hypersensitivity to gemcitabine or to any of the excipients.

8. Any one of the following currently or in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack; symptomatic pulmonary embolism; congenital long QT syndrome, torsades de points, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, or QTc interval >470 msec at screening.

9. Concurrent administration of herbal preparations.

10. Use of oral anticoagulants. Use of subcutaneous anti-coagulation is allowed. Concurrent use of potent or moderate inhibitors or inducers of CYP3A4 and/or CYP2C8.

11. Active and clinically significant bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) -related illness.

12. History of interstitial lung disease, or slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.

13. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior) or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

14. Pregnant female patients; breastfeeding female patients; males patients with partners currently pregnant, male patients able to father children and female patients of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for 28 days after last dose of PF-04136309, and for 6 months after last dose of nab-paclitaxel, gemcitabine, or both.

15. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.

4.3. Lifestyle Guidelines

4.3.1. Contraception

In this study, male subjects who are able to father children and female subjects who are of childbearing potential will receive PF-04136309, which the teratogenic risk is currently unknown and chemotherapeutic agents that have been associated with teratogenic risk. Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 28 days after the last dose of PF-04136309, and for 6 months after last dose of nab-paclitaxel, gemcitabine, or both. The investigator or his or her designee, in consultation with the subject, will confirm the subject has selected 2 appropriate methods of contraception for the individual subject and his or her partner from the list of permitted contraception methods (see below) and instruct the subject in their consistent and correct use. Subjects need to affirm that they meet the criteria for the correct use of at least 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, transdermal, or implanted hormonal methods of contraception are allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets the criteria for non-childbearing potential as described below.

   Female subjects of non-childbearing potential must meet at least one of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

      All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/team study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

5.1.1. Phase 1b Dose-finding

In Phase 1b (dose-finding study), eligible patients will be enrolled to receive PF-04136309 in combination with nab-paclitaxel + gemcitabine in an open-labeled, unblinded manner. Patients will be successively assigned to the next available treatment slot at a PF-04136309 dose level decided on after the previous cohort's safety evaluation and ongoing observations of earlier enrolled patients. In the dose finding study, patients will be enrolled in cohorts of 2 to 4 patients, starting with 750 mg BID of PF-04136309 for the first cohort. A higher dose level of PF-04136309 at 1000 mg BID may be explored.

Dose level allocation in Phase 1b will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The Investigator or designee will enroll the patient according to the procedure described in the Study Manual. The Sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other study-related documentation or correspondence referencing that patient. No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- confirmation of the patient's enrolment;
- specification of the dose level for that patient; and
- permission to proceed with dosing the patient.

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

5.1.2. Phase 2 Randomized

In the Phase 2 randomized double blinded placebo control study, patients will be assigned to one of the following treatments following a randomization ratio 1:1:

- Arm A: Nab-Paclitaxel + Gemcitabine + PF-04136309 oral daily BID.
- Arm B: Nab-Paclitaxel + Gemcitabine + Placebo oral daily BID.

Randomization will be stratified by site (two strata: the site of University of Rochester, and other sites).

The doses of nab-paclitaxel and gemcitabine will be as described in Section 5.4.2 and Section 5.4.3. The dose of PF-04136309 will be the RP2D determined in the Phase 1b portion of the study.

During the randomized portion of the study, the assignment of patient identification numbers and the allocation of patients to treatment groups may be managed via the use of an automated Interactive Response Technology (IRT) system or another equivalent system provided by the Sponsor. Further information on the procedure for patient management for the Phase 2 portion of the study will be described in the Study Manual.

Treatment allocation will be blinded to the patient, investigator and the sponsor.

5.2. Patient Compliance

5.2.1. PF-04136309 and Placebo

Patients will be instructed to record daily administration of study drug (PF-04136309 or placebo) in a patient diary provided by the Sponsor. Missed or changed doses and dates of all missed doses need to be annotated.

Patients will be required to return all unused study medication at the beginning of each cycle. The number of tablets (PF-04136309 or placebo) returned by the patient at the end of the cycle will be counted, documented and recorded. Compliance of outpatient dosing will be assessed by site personnel by review of the patient's dosing diary and by tablet counts for remaining tablets at each visit.

Any deviations in compliance should be discussed by the investigator and Pfizer study team and an assessment will be made as to whether the patient may continue in the study or be withdrawn.

5.2.2. Nab-paclitaxel and Gemcitabine

For assessing compliance of nab-paclitaxel and gemcitabine, the site should complete the required dosage Preparation Record located in the Study Manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Sponsor.

5.3. Investigational Product Supplies

Additional information can be found in the Investigational Product Manual.

5.3.1. Dosage Form(s) and Packaging

PF-04136309 and placebo will be supplied by Pfizer as formulated 125 mg tablet or matching placebo tablet for oral administration. The sponsor will supply the oral drug formulation to sites in high-density polyethylene (HDPE) bottles. Labeling will occur according to local regulatory requirements.

In each cycle, nab-paclitaxel will be administered first as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 followed by 1 week of no treatment (Schedule 3/1). The dose of nab-paclitaxel will be 125 mg/m^2.

Gemcitabine will be administered immediately after nab-paclitaxel, as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each cycle, followed by 1 week of no treatment (Schedule 3/1). The dose of gemcitabine will be 1000 mg/m^2.

Nab-paclitaxel and gemcitabine to be administered during this study will be branded or generic product available in the local region. Nab-paclitaxel and gemcitabine will be procured by the study sites unless local regulations or other limitations require direct provision of background therapy by the Sponsor. Nab-paclitaxel and gemcitabine are to be stored, prepared and administered according to locally approved product labeling.

Study centers will receive a supply of Clinical Trial Material upon screening or confirmation of study enrollment of the first patient along with instructions on how to confirm drug receipt. Resupplies will be made during the course of the study based on patient need. The details on drug supply will be provided in the Study Manual. The study monitor should be contacted for any issues related to drug supplies.

5.3.2. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.3.2.1. PF-04136309 and Placebo

Site personnel must ensure that patients clearly understand the dosing directions for self-medication. A Patient Dosing Diary and Instruction Card will be included in the Study Manual and will provide detailed instructions for daily administration of study drug and will be used for patients to record dosing compliance. An example of the diary is provided in Appendix 4.

5.3.2.2. Nab-paclitaxel

Nab-paclitaxel will be prepared and administered according to the package insert and product labeling. Inject the appropriate amount of reconstituted nab-paclitaxel into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized di-(2-ethylhexyl)phthalate (DEHP)-free solution containers or administration sets is not necessary to prepare or administer nab-paclitaxel infusions. The use of an in-line filter is not recommended.

Nab-paclitaxel is a cytotoxic drug, and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling it. The use of gloves is recommended. If nab-paclitaxel (lyophilized cake or reconstituted suspension) contacts the skin, the skin must be washed immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If nab-paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

5.3.2.3. Gemcitabine

Gemcitabine will be prepared and administered according to see the package insert and product labeling.

Caution should be exercised in handling and preparing gemcitabine for injection. The use of gloves is recommended. If a solution of gemcitabine for injection contacts the skin or mucosa, the skin must be washed immediately and thoroughly with soap and water, or the mucosa must be rinsed with copious amounts of water alone. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

5.4. Administration

5.4.1. PF-04136309

The starting dose for PF-04136309 in the Phase 1b portion will be 750 mg BID. PF-04136309 is to be administered orally, on a continuous basis, twice daily (BID) in 28-day cycles. Available dose levels are described in Table 5.

PF-04136309 or placebo should be taken approximately the same time each day, approximately 12 hours apart. The allowable treatment window for PF-04136309 or placebo is ±4 hours. PF-04136309 dosing should not be taken sooner than 8 hours and no more than 16 hours following the last PF-04136309 dosing. The patient will be reminded not to take their dose at home on clinic days, but to bring their bottle into clinic so that study drug may be administered after study visit assessments are completed, PK samples have been collected and nab-paclitaxel and gemcitabine have been administered prior to the PF-04136309 or placebo dosing.

Patients will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

Patient should be instructed to take their study medication, PF-04136309 or placebo, with at least 6-ounces (180 mL) of water. There is no requirement for fasting as a result of the A9421019 study, which evaluated the effect of food on the PK of PF-04136309, indicating no significant effect of food on the PK of PF-04136309.

If a patient misses a day of treatment, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed.

If a patient vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses as prescribed.

If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of PF-04136309.

On days where the morning dose of PF-04136309 or placebo is held due to a specific study visit (Cycle 1 Days 1, 2, 3, 4, 8, 15, 16, and 22, and subsequent cycle visits Days 1, 8 and 15) the 2nd BID dosing should be taken no sooner than 8 hours, and no later than 16 hours post the first BID dosing (allowable treatment window ±4 hours).

Treatment will continue until PD, unacceptable toxicity or patient refusal, whichever occurs first. If PD occurs during treatment, continuation of one or more combination agents may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor.

5.4.2. Nab-paclitaxel

Treatment will be administered in 28-day cycles. In each cycle, nab-paclitaxel will be administered first, as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 followed by 1 week of no treatment (Schedule 3/1). The dose of nab-paclitaxel will be 125 mg/m^2. Administer nab-paclitaxel according to the package insert and product labeling.

Treatment will continue until PD, unacceptable toxicity or patient refusal, whichever occurs first. If PD occurs during treatment, continuation of one or more combination agents may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor.

5.4.3. Gemcitabine

Treatment will be administered in 28-day cycles. Gemcitabine will be administered immediately after nab-paclitaxel, on Days 1, 8 and 15 of each cycle followed by 1 week off treatment (Schedule 3/1). The dose of gemcitabine will be 1000 mg/m^2. Administer gemcitabine according to the package insert and product labeling.

Treatment will continue until PD, unacceptable toxicity or patient refusal, whichever occurs first. If PD occurs during treatment, continuation of one or more combination agents may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor.

5.4.4. Recommended Dose Modifications

Every effort should be made to administer study treatment on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in 3 ways:

Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, of study drugs during a given treatment cycle.

Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.

In the next cycle: dose reduction may be required in a subsequent cycle based on worst toxicity experienced in the previous cycle.

5.4.5. Dosing Interruptions/Delays/Reductions

5.4.5.1. PF-04136309-Induced Dose Interruptions and Delays

PF-04136309 does not have to be interrupted in case of hematologic toxicity until Grade 3 or peripheral neurotoxicity. PF-04136309 should be interrupted in case of ≥ Grade 2 non-hematologic or non-peripheral neurological toxicity, potentially due to PF-04136309.

5.4.5.2. Chemotherapy-Induced Dose Interruptions and Delays

A new chemotherapy cycle (both agents) may not start until the following parameters have been met:

- ANC ≥1,500/μL;
- Platelets count ≥100,000/μL;
- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the Investigator discretion, Grade ≤2, if not considered a safety risk for the patient).

PF-04136309 and gemcitabine cannot be administered until the following parameters have been met:

- AST and ALT ≤2.5 x ULN; ≤5.0 x ULN if liver involvement by the tumor.

In addition, gemcitabine cannot be administered until:

- Creatinine ≤1.0 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If starting of the next cycle is delayed for toxicities attributable only to nab-paclitaxel and/or gemcitabine, the administration of PF-04136309 should not be interrupted and may continue until the next administration of chemotherapy.

Nab-paclitaxel may be administered if hematological toxicities are recovered to the criteria reported above, despite the fact that liver and renal function tests do not meet the criteria for re-treatment, as outlined above.

Gemcitabine administration must be omitted until liver and renal function tests return to the above reported value. If liver and renal toxicities persist beyond 14 days, gemcitabine as well as nab-paclitaxel and PF-04136309 should be interrupted.

If a treatment interruption continues beyond Day 28 of the current cycle, then the day when nab-paclitaxel and/or gemcitabine are restarted will be counted as Day 1 of the next cycle.

Overall, if toxicities (hematologic and non-hematologic) do not revert to acceptable levels as defined above, chemotherapy resumption must be delayed. The 14 days of treatment delay does not include the one week of no treatment in each 3/1 cycle of chemotherapy. A treatment delay or interruption of more than 14 days due to lack of recovery will result in discontinuation of the patient from treatment unless discussed and agreed with the sponsor.

Treatment resumption for patients recovering from treatment-related toxicities after 14 days can be considered only if there is a reasonable evidence of clinical benefit from one or more compounds, the safety of continuing one or more compounds is adequate, and after discussion with the Sponsor (including a discussion of which treatment will continue).

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Dose Interruptions/Delays/Reductions, Section 3.7.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in section Dose Reductions, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

5.4.6. Dose Reductions

However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

PF-04136309, nab-paclitaxel or gemcitabine doses may need to be reduced when treatment is resumed following dose interruption or cycle delay due to toxicity.

Table 5. Available Doses lists available doses for dose modifications of each drug.

Table 5. Available Doses

PF-04136309 or Placebo (mg/BID)		Nab-Paclitaxel (mg/m^2)		Gemcitabine (mg/m^2)
750 or 1000		125		1000
500		100		800
250		75		600

No specific dose reductions are recommended for Grade 1 and 2 treatment-related toxicities, with the exception of some drug-related, non-hematological toxicities that are Grade ≥2, as reported in Table 4. However, Investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Dose reductions from the starting dose of 1 or 2 doses will be allowed, depending on the type and severity of toxicity encountered. Patients requiring dose reductions to exposure levels of PF-04136309 <250 mg, nab-paclitaxel <75 mg/m^2, gemcitabine <600 mg/m^2 will be discontinued from the treatment and entered into the follow up phase, unless otherwise agreed between the Investigator and the Sponsor.

All dose modifications/adjustments must be clearly documented in the patient's source notes and CRF.

Recommended dose reductions for neutropenia and/or thrombocytopenia at the start of a cycle or within a cycle are illustrated in Table 3.

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during Cycles 1 and 2 but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[42] G-CSF may be used prophylactically after completion of 2 treatment cycles.

Recommended dose reductions for non-hematological toxicities at the start of a cycle or within a cycle are illustrated in Table 4.

5.5. Investigational Product Storage

The investigator, or an approved representative (eg, pharmacist) will ensure that all investigational products, including any comparator and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the dosage and administration instructions (DAI), package insert, or equivalent for storage conditions of the product once reconstituted and/or diluted.

Storage conditions stated in the single reference safety document (SRSD) (eg, investigator brochure [IB], core data sheet [CDS], United States package insert [USPI], summary of product characteristics [SPC], or local product document [LPD]) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

The Investigational Product Manual should be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions. More specific details will be provided to the sites separately.

Site staff will instruct patients on the proper storage requirements for take home study treatment.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. Patients will be required to return all bottles of study medication at the beginning of each 4 week period. The number of tablets remaining will be documented and recorded. Patient compliance is covered in Section 5.2.

5.7. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as non-drug interventions (eg, paracentesis) received by patients from screening until the end of study visit must be recorded on the CRF.

Because inhibition of CYP3A4 isoenzymes may increase PF-04136309 exposure leading to a potential increases in toxicities, the use of known strong/moderate inhibitors *(Strong CYP3A4 Inhibitors:* grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, nefazodone, lopinavir, troleandomycin, mibefradil, conivaptan; *Moderate CYP3A4 inhibitors:* Erythromycin, verapamil, atazanavir, fluconazole, darunavir, diltiazem, delavirdine, aprepitant, imatinib, tofisopam, ciprofloxacin, cimetidine)[41] are not permitted from 10 days prior to the first dose of PF-04136309 until study treatment discontinuation (OR) caution should be warranted with co-administration with PF-04136309.

PF-04136309 metabolism may be induced when taking strong CYP3A4 inducers (eg, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St. John's Wort)[41] resulting in reduced plasma concentrations. Therefore co-administration of PF-04136309 in combination with these and other strong CYP3A4 inducers is not permitted from 10 days prior to the first dose of PF-04136309 until study treatment discontinuation (OR) caution should be warranted with co-administration with PF-04136309.

Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (eg, rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

5.8.1. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while patients are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PF-04136309 with radiotherapy, PF-04136309 treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment 7 days after completion of radiotherapy.

5.8.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

5.8.3. Hematopoietic Growth Factors

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

5.8.4. Anti-Diarrheal, Anti Emetic Therapy

Supportive care may include premedication with antiemetics to limit gemcitabine treatment-related nausea and vomiting. Primary prophylaxis of diarrhea, nausea and vomiting is permitted in the first cycle. Primary prophylaxis in subsequent cycles is at the investigator's discretion. The choice of the prophylactic drug is up to the investigator with sponsor approval and assuming the drug is not included in the Concomitant Treatment(s) section, as well as the duration of treatment, assuming there is no known or expected drug-drug interaction. If so, then it must be approved by the sponsor.

5.8.5. Anti-inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatment(s) section.

5.8.6. Corticosteroids

Chronic, systemic corticosteroid use for palliative or supportive purposes is not permitted. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

5.8.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-04136309 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-04136309 is recommended at least 14 days prior to surgery. Post-operatively, the decision to reinitiate PF-04136309 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

All patients being considered for the study and eligible for screening must sign an informed consent for the study before completing any study-specific procedures. A patient identification number will be assigned. The investigator (or appropriate delegate at the site) will obtain informed consent from each patient in accordance with the procedures described in the Schedule of Activities and Section 12.3 on Patient Information and Informed Consent. Informed consent must be obtained prior to undergoing any study specific procedures.

Patients will be screened within 28 days prior to administration of the study treatment to confirm that they meet the patient selection criteria for the study.

Medical history will include the date of diagnosis and information on prior anti-tumor treatments, surgeries, radiotherapy and recurrence date.

Patients will be asked about any signs and symptoms experienced within 14 days prior to study entry. Baseline signs and symptoms will be recorded on the BSS Adverse Events (AEs) case report form (CRF) page.

The required screening assessments and laboratory tests are summarized in the Schedule of Activities and Section 7.1.3. Following completion of the screening assessments and confirmation of eligibility, patients may be enrolled.

6.2. Study Period.

For treatment period procedures, see Schedule of Activities and ASSESSMENTS Section.

6.3. End of Treatment

For end of treatment procedures, see Schedule of Activities and ASSESSMENTS Section. End of Treatment procedures should be completed if not done in the last calendar week. Tumor assessments should be repeated at the End of Treatment visit if more than 8 weeks have passed since the last evaluation.

6.4. Follow-up Visit

For follow-up procedures, see Schedule of Activities and ASSESSMENTS Section.

At least 28 days, and no more than 35 days after discontinuation of treatment, patients will return to undergo review of concomitant medications and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. When the study treatment is discontinued for reasons other than disease progression or patient refusal, patients will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) patient refusal or (c) start of another anti-cancer treatment, (whichever occurred first).

In the event a patient is unable to return to the clinic for the follow-up visit, telephone contact with the patient to assess adverse events and concomitant medications and treatment is expected. If laboratory assessments are needed to follow-up unresolved adverse events, retrieval of assessments performed at an institution local to the patient is acceptable.

6.5. Patient Withdrawal

The reason for a patient's discontinuation from treatment will be documented in the end of study/withdrawal CRF. Patients will be followed for at least 28 days after the last dose of study drug for adverse events.

Patients may withdraw from treatment at any time at their own request, they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Adverse event;
- Medication error without associated adverse event;
- Significant protocol violation;
- Lost to follow-up;
- Patient no longer willing to participate in study;
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Patient refusal for further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable and follow-up with the patient regarding any unresolved adverse events (AEs).

If the patient refuses further visits, and the patient withdraws consent for disclosure of future information or for further contact, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.6. Survival Follow-up

After treatment discontinuation, patient survival status will be collected every 3 months until death (telephone contact acceptable).

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

Safety assessments will include collection of adverse events (AEs), serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

7.1.1. Pregnancy Testing

Nonclinical fertility and early embryonic and pre- and postnatal development studies have not been completed with PF-04136309. In the absence of definitive studies, the potential risks to the developing embryo and foetus are undetermined; therefore, PF-04136309 should not be administered in pregnant women. Moreover, PF-04136309 should not be administered to women of childbearing potential in the absence of 2 forms of contraception. In addition, pregnancy testing prior to enrollment and at follow up will be employed for any suitable patient participating in the clinical study.

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment-once at the start of screening and once at the baseline visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit within 5 days after the first day of the menstrual period counting the first day as day 1 > before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from treatment but may remain in the study. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE version 4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the BSS adverse events CRF page.

7.1.3. Laboratory Safety Assessment

7.1.3.1. Hematology and Blood Chemistry

Hematology and blood chemistry tests will include the parameters presented in Table 6 Blood tests will be drawn at the time points described in Schedule of Activity table and analyzed at local laboratories. Additional blood tests may be performed at the investigator's discretion for the purpose of planning treatment administration, dose modification, or following adverse events. There is no need to repeat hematology, chemistry, coagulation or urinalysis samples on Cycle 1 Day 1 (C1D1) if screening assessment performed within 7 days prior to that date.

Table 6. Laboratory Test

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs or %) Eosinophils (Abs or %) Monocytes (Abs or %) Basophils (Abs or %) Lymphocytes (Abs or %)	BUN/urea and Creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST, ALT Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein Magnesium Phosphorous or Phosphate	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a] Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing) Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	FSH[b] HbsAg, HbcAb, HCV[c,d] HIV[c,d] β-hCG[e] IgG, IgA, and IgM[f] CA-19.9[g] Biomarker Collection[h]
Addition Test Coagulation	Additional Tests (Needed for Hy's law)***		
PT or INR PTT	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. At Screening only, in females who are amenorrheic for at least 12 consecutive months.
c. At Screening only.
d. Viral disease screening test to be conducted by local laboratory where required by local regulations or if warranted by patient history.
e. Serum or urine β-hCG for females of childbearing potential.
f. Samples collected at Cycle 1 Days 1, 8 and 15, and at subsequent Cycles Days 1 and 15, EOT and follow-up.
g. Samples collected at Cycle 1 Days 1 and 22 and at subsequent even Cycles on Day 1 and at EOT.
h. See Table 7.

*** For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

HBsAg, HbcAb, HCVAb, and HIV testing to demonstrate eligibility to be conducted by local laboratory where required by local regulations or if warranted by patient history. In all other countries, testing should be considered if a patient is at risk for having undiagnosed infection (for example due to history of injection drug use or due to geographic location). Testing will be conducted by the local laboratory.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination of major body systems to include weight, vital signs (BP, PR to be recorded in the sitting position after approximately 5 minutes of rest), assessment of ECOG performance status and height; height will be measured at screening only. Weight will be obtained at Screening, Days 1, 8, and 15 of every cycle, and at the EOT and Follow-up visits. A neurological examination will be performed as part of the physical examination at Cycle 1 Day (prior to dosing), Day 1 on all subsequent cycles (prior to dosing), EOT, and at the Follow-up visit (see Appendix 5).

7.1.5. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) in combination with the Chemotherapy-Induced Peripheral Neuropathy-20 Questionnaire (EORTC QLQ-CIPN20)

Questionnaires will be completed prior to any study or medical procedure on Cycle 1 Day 1 (-2 day window), Day 1 of all subsequent cycles, and at the End of Treatment visit. One final questionnaire will be completed 4 weeks after discontinuation of IP during the Follow-up Visit. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. Interviewer administration in the clinic may be used under special circumstances.

7.1.6. Triplicate (12-Lead) Electrocardiogram

Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (>480 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >480 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 480 msec. If QTcF interval reverts to less than 480 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 480 msec the investigational product will be held until the QTcF interval decreases to ≤480 msec and to within 20 msec of baseline. Additionally, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. Patients will then restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to 480 msec after 2-weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

After Cycle 3, ECGs can be performed as clinically indicated. All ECG collection time points are with respect to PF-04136309 morning dosing.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). A 15-min window for each ECG collection is allowed around the nominal ECG time point.

7.2. Pharmacokinetics Assessments

7.2.1. Blood for PF-04136309 Pharmacokinetic Analysis

Phase 1b Dose Escalation Cohorts: Blood samples for determination of the PF-04136309 concentrations will be collected at the following timepoints:

- Cycle 1 Day 1: within 6 hours prior to the first PF-04136309 dose on C1D1;
- Cycle 1 Day 2 and Day 8: within 30 minutes prior to the morning dose of PF-04136309;
- Cycle 1 Day 15: 0 hour (within 30 minutes prior to the morning dose of PF-04136309, and 0.5, 1, 2, 3, 4, and 6 hours after the morning dose;
- Cycle 1 Day 16: within 30 minutes prior to the morning dose of PF-04136309;
- Day 1 Cycle 2 and subsequent cycles: within 30 minutes of the morning dose of PF-04136309;
- End of Treatment.

Phase 2: Blood samples for determination of the PF-04136309 concentrations will be collected at the following timepoints:

- Cycle 1 Day 1: within 6 hours prior to the first PF-04136309 dose on Cycle 1 Day 1;
- Cycle 1 Day 2, Day 8, Day 15: within 30 minutes prior to the morning dose of PF-04136309;
- Day 1 of Cycle 2 and subsequent cycles: within 30 minutes prior to the morning dose of PF-04136309;

- End of treatment.

On days when patients have clinical visits where PK assessments are to be obtained, the morning dose of PF-04136309 should be held (NOT taken) prior to the study visit. On those days, the PF-04136309 morning dose can be taken after the study procedures required immediately prior to the PF-04136309 morning dose have been performed (including completion of the nab-paclitaxel and gemcitabine intravenous administration).

A PK sample should be collected matched with a biomarker sample any time an unscheduled/optional biomarker sample or FNA or core needle biopsy (±2 hours) is collected.

PK samples collected from patients randomized to receive nab-paclitaxel + gemcitabine + placebo will not be analyzed.

Blood samples (4 mL whole blood) sufficient to provide at least 1 mL of plasma will be collected into appropriately labeled tubes containing K2-EDTA as an anticoagulant for PK analysis of PF-04136309 as outlined in the Schedule of Activities (PHARMACOKINETIC AND PHARMACODYNAMIC SAMPLING SCHEDULE). On days when patients have clinical visits where PK assessments are to be obtained, the morning dose of PF-04136309 should be held (NOT taken) prior to the study visit, until the pre-dose PK sample on the day has been collected. The exact time of the morning dose administration on the days of PF-04136309 PK sampling will be recorded in the CRF. The exact time of PK sample collection will also be recorded in the CRF. PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AE's and the date and time of blood sample collection and of last dosing prior to PK collection documented in the CRF.

Blood samples for PF-04136309 PK will be placed on ice and centrifuged at 4°C to obtain plasma within 10 minutes of blood sample collection. Plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

Where noted in the Schedule of Activities, blood samples for PF-04136309 concentrations will be collected at approximately the same time as other assessments such as pharmacodynamic samples, ECGs and bone marrow aspirate collections etc., wherever possible.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, patient, and sponsor.

PK samples collected from patients receiving PF-04136309 will be assayed for PF-04136309 using a validated analytical method in compliance with Pfizer standard operating procedures. PK samples collected from patients randomized to receive nab-paclitaxel, gemcitabine plus Placebo (ARM B in Phase 2) will not be analyzed. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

As part of the understanding of the PK of investigational product, PK samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods of PF-04136309. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.3. Biomarker and Pharmacodynamic Assessments

Optional, paired collections of core needle biopsy from a metastatic site or fine-needle aspirates (FNAs) from the primary tumor tissue (if sample collection from a metastatic site is not viable) will be performed on at least 12 patients in each treatment arm at screening and at the end of Cycle 1 Day 28 (±7 days) or at the end Cycle 2 Day 28 (±7 days), study Day 56, if sample not collected at C1D28. Core-needle biopsies or FNAs will be optional for patients participating in the Phase 1b cohorts. For Phase 2 dose expansion cohorts, core-needle biopsies or FNAs will be optional; however, at least 12 paired biopsies will have to be available and fully assessable in each treatment arm, Arm A and Arm B, to allow the comparison. An optional bone marrow aspirate (BMA) will be performed on at least 12 patients at Screening and at the end of Cycle 1 Day 28 (±7 days) or at the end Cycle 2 Day 28 (±7 days), study Day 56 if sample not collected at C1D28.

Samples will be analyzed using the type of assays as described in Table 7 for evidence of PF-04136309 pharmacodynamic activity and immunophenotyping of tumors and patients. Additional pathway-related markers (eg, a,b,c) may be included as pre-clinical studies or literature reports further elucidate the mechanism of action of PF-04136309 or the relevant signaling pathway or as new technology becomes available.

Table 7 summarizes representative assays to be used and the source of the samples. Refer to the Schedule of Activities for details pertaining to specific days of sample collection and to the Lab Manual for details of sample preparation.

Table 7. Biomarker Collections and Analyses

Biomarker	Sample Type	Analysis
Target Occupancy (3 mL)	Whole Blood	Ex vivo inhibition of CCL2-induced, ERK phosphorylation by flow cytometry
Immune Cell Phenotypes (10 mL)	Core needle biopsy from a metastatic site or FNA from the primary tumor tissue; bone marrow aspirates; peripheral blood	CD14+CCR2+ monocytes and other immune cell phenotypes by flow cytometry
CCL2, Cytokines, Chemokines and immune regulatory cytokines (4.5 mL)	Whole Blood for Plasma preparation	The CCR2 ligand, CCL2, and other immunomodulatory chemokines and cytokines by immunoassay

Biomarker	Sample Type	Analysis
Transcriptional Profile RNA Profiling Peripheral Blood (2-2.5 mL)	Core needle biopsy from a metastatic site or FNA from the primary tumor tissue; bone marrow aspirates; peripheral blood (RNA)	RNA will be analyzed for expression profile of immune- and tumor-related transcripts.
T cell Repertoire in Peripheral Blood (4 mL)	Core needle biopsy from a metastatic site or FNA from the primary tumor tissue; peripheral blood (DNA)	DNA will be submitted to TCR sequencing analysis
Tumor Epitope Profile	Core needle biopsy from a metastatic site or FNA from the primary tumor tissue (DNA)	DNA will be submitted to whole exome sequencing analysis

7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases.

CT or MRI scans are to be performed every 8 weeks – efficacy assessments start at the end of Cycle 2 Day 28, prior to the start of Cycle 3. The allowable time window for disease assessments is ±7 days while on treatment and up to -7 days for screening (ie, the screening time window is up to 35 days prior to registration). Tumor assessment should be repeated at the end of treatment visit if more than 8 weeks have passed since the last evaluation. When the study treatment is discontinued for reasons other than disease progression or patient refusal, patients will be followed and have tumor assessments performed every 8 weeks until (a) disease progression or death, (b) patient refusal or (c) start of another anti-cancer treatment, whichever occurs first. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. For patients enrolled in the Phase 2 cohorts, responses of CR or PR must be confirmed by repeat assessment no less than 4 weeks after the criteria for response are first met. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Assessment of response will be made using RECIST version 1.1 (Appendix 1).

All patients' files and radiologic images must be available for source verification and for potential peer review. Central review of imaging studies and clinical information documenting disease status will be performed to verify recurrence of mPDA or occurrence of secondary tumor.

It is important to the integrity of the study that all imaging studies are forwarded to the central review laboratory as each patient enrolls and progresses through the study. Materials to be forwarded for independent review are all imaging studies performed on study, preferably in digital format on compact disc, optical disc, or via process as specified in the Core Imaging Study Manual. All digital media must be in Digital Imaging and

Communications in Medicine (DICOM) format. Films may be forwarded for review if necessary; all films must be originals (second original films acceptable) rather than copies of films. Further information on materials to be forwarded for independent review is provided in the Core Imaging Study Manual.

7.5. Banked Biospecimens

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomics/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomics/biomarker research analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which case any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical study.

A 4 mL blood sample Prep D1 (K_2 edetic acid (ethylenediaminetetraacetic acid) (EDTA) whole blood collection optimized for DNA analysis) will be collected at the Screening and Cycle 3, Day 1 (pre-dose) visit to be retained for potential pharmacogenomics/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee

decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Banked Biospecimen will be collected from all patients unless prohibited by local regulations. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.5.1. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions;
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in Section 7.3 will be used. Patients may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.6. Assessment of Suicidal Ideation and Behavior

This section is not applicable.

7.7. Triggered Requirements

This section is not applicable.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the

AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE) grade 5 (see the section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase(AST) and/or alanine aminotransferase(ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

- For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller);

Concurrent with:

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All

cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;

- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;

- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

Investigators will report adverse events using concise medical terminology (verbatim) as well as collect on the CRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03, Publish Date: 14 June 2010, *http://ctep.cancer.gov/reporting/ctc.html*) listed in the Cancer Therapy Evaluation Program.

The investigator will use the following definitions of severity in accordance with the current CTCAE version to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be

provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the

terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.15. Medical Device Complaint Reporting Requirements

This section is not applicable.

8.16. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Data Analysis

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. The information may include details of missing and, if applicable, unused and spurious data. Deviations from the statistical plan will be reported in the clinical study report.

This study is divided into 2 phases:

- Phase 1b: dose finding phase, and
- Phase 2: randomized, double blinded, placebo controlled study.

9.1.1. Phase 1b

Patients will participate in a dose-escalation part aimed at estimating the MTD and RP2D. The sample size for this component of the study will vary depending on the number of DLTs observed.

9.1.2. Phase 2

In the Phase 2 randomized study PFS will be the primary endpoint.

This randomized Phase 2 study is designed to determine whether Arm A is superior to Arm B. This trial is designed to detect a hazard ratio of 0.55 with 80% power at a two-sided 0.2 level of significance.

9.1.3. Analysis Sets

Data Analysis will be performed on the following analysis population.

1. Safety analysis set.

   The safety analysis set includes all enrolled patients who receive at least one dose of study treatment.

2. Full analysis set.

   The full analysis set includes all randomized patients. This is equivalent to the ITT (intent-to-treat) population.

3. Per protocol analysis set (evaluable for MTD and RP2D).

   The per protocol analysis set includes all enrolled patients who receive at least one dose of study treatment and who do not have major protocol deviations during first cycle. Patients with important protocol deviations during the first cycle of treatment are not evaluable for the MTD or RP2D assessment and will be replaced as needed. Important protocol deviations may include failure to satisfy major entry criteria (eg, confirmation of the target disease; signed informed consent) or use of other anticancer treatments during the active treatment and disease follow-up phases other than as defined/allowed in this protocol.

4. Modified Intent-to-Treat (mITT) Population.

   The modified intent-to-treat (mITT) is the analysis population that will follow the ITT principle and include subjects receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment. The mITT population may be used for PD, biomarkers analyses and anti-tumor assessment.

5. PK analysis sets

   The PK concentration population is defined as all patients receiving PF-04136309 treatment, have no major protocol deviations affecting the PK assessment, and have at least 1 post-dose sample with measurable drug concentration.

6. Tumor Biopsies analysis sets

   Tumor biopsies will be performed in the Phase 2 randomized study pre-treatment and post- treatment after 1 or 2 cycles. At least 12 paired biopsies will have to be available and fully assessable in each arm, arm A and arm B, to allow the comparison.

9.2. Statistical Methods and Properties

9.2.1. Phase 1b

Patients will participate in a dose-escalation part aimed at estimating the MTD and RP2D. The sample size for this component of the study will vary depending on the number of DLTs observed. This study phase has been designed to establish the Maximum Tolerated Dose (MTD) defined as the dose that yields approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (Equivalence Interval) 22.5% to 32.5%. The 27.5% target and the Equivalence Interval are chosen based on safety considerations and is considered appropriate based on simulations and expert input (see Sections 9.2.3 and 9.2.4).

9.2.2. Statistical Methods for Dose Escalation/De-Escalation (Phase 1b)

Many alternative designs have been proposed to the standard 3+3 design for Phase 1 dose escalation studies that improve its accuracy, efficiency and statistical validity.

The modified toxicity probability interval (mTPI) design[43] uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.275).

The prior distribution of DLT is set as a beta (0.5,0.5) and the threshold probability for early termination and dose exclusion is set to 0.95 as suggested in the mTPI design.[43] Doses with an incidence of DLT>33% (eg, 4 out of 10) cannot be selected as MTD although is allowed by the mTPI method. If the toxicity rate of the currently used dose level is far smaller than 27.5%, the mTPI will recommend escalating the dose level; if it is close to 27.5%, the mTPI will recommend continuing at the current dose; if it is far greater than 27.5%, the mTPI will recommend de-escalating the dose level. Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions. Target size for each cohort will be n= 2 to 4 patients as described in mTPI design.[43] All the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table. The decision rules to "dose escalate" (E), "no change in dose" (S), "dose de-escalate" (D) or "dose de-escalate, unacceptable toxicity" (U) are described in Table 8. Decision Rules**.**

Cohorts of patients could receive doses already tested but a dose that is associated with decision "Dose de-escalate, unacceptable toxicity" cannot be revisited and no more patients should be treated at this dose or higher doses for the remainder of the trial.

Table 8. Decision Rules

	Number of Patient Treated at a Dose Level													
Number of Patients Having DLT	n=2	n=3	n=4	n=5	**n=6**	**n=7**	**n=8**	**n=9**	**n=10**	**n=11**	**n=12**	**N=13**	**N=14**	**N=15**
0	E	E	E	E	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
1	S	S	S	E	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
2	U	D	S	S	**S**	**S**	**S**	**S**	**S**	**S**	**E**	**E**	**E**	**E**
3		U	U	D	**D**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**E**
4			U	U	**U**	**U**	**D**	**D**	**D**	**D**	**S**	**S**	**S**	**S**
5				U	**U**	**U**	**U**	**U**	**D**	**D**	**D**	**D**	**D**	**S**
6					**U**	**U**	**U**	**U**	**U**	**U**	**U**	**D**	**D**	**D**
7						**U**	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**U**

D: De-escalate the dose; E: Escalate the dose; S: Stay at the dose; U: Unacceptable toxicity
Note: Starting dose is 750 mg BID. Escalation to a higher dose (eg 1000 mg BID) will require that at least 6 patients are dosed at 750 mg BID and no more than 1 experienced a DLT.

9.2.3. Statistical Method for Estimating the MTD and RP2D (Phase 1b)

An MTD may not be identified, as DLTs may not be frequently observed after administration of this investigational agent. Dose escalation may continue up to a predefined Maximum Feasible Dose (MFD) (eg 1000 mg) and the escalation is halted without a maximum tolerated dose (MTD) estimate. The study will continue accruing until one of the three stopping conditions below is triggered.

The algorithm will stop if any of the following criteria is met:

1. MTD or RP2D has been identified with sufficient accuracy: at least 6 to 12 patients have been accumulated on a dose that is currently estimated to be the MTD or RP2D; or

2. All doses explored appear to be overly toxic.

Due to binomial data variability in small samples, DLTs may be observed in a first cohort(s) by chance even when the true Probability (DLT) is fairly low. This could result in the estimated posterior DLT rate to exceed the targeted very early in the trial, triggering an early stop when very few patients (eg 3) have been treated. To prevent stopping the trial prematurely in such cases, a step-down option with a lower dose of 500 mg added to the dose grid.

9.2.4. Phase 2

In the Phase 2 randomized study PFS will be the primary endpoint.

This randomized Phase 2 study is designed to determine whether Arm A is superior to Arm B. This trial is designed to detect a hazard ratio of 0.55 with 80% power at a two-sided 0.2 level of significance.

9.3. Sample Size Determination

Phase 1b: The number of patients to be enrolled in the study will depend upon the observed safety profile, which will determine the number of patients at each dose level and the number of dose levels explored. It is envisaged that the maximum sample size at the RP2D would be N=12 (see Section 9.2.3). To further evaluate safety and pharmacodynamics, the number of patients enrolled during this part of the study (Phase 1b) may be N up to 20.

Phase 2: Ninety-two (92) patients will be randomized in a 1:1 ratio Arm A versus Arm B. Median PFS in patients enrolled in the control arm (Arm B) is expected to be approximately 5.5 months. A total of 92 patients and 57 events are required for a log-rank test to have an overall 1-sided significance level of 0.1 (alpha=0.2) and power of 0.80. This assumes an 82% improvement in median PFS from 5.5 months to 10 months and an HR=0.55. Predicted accrual is approximately n=7 patients per month and the predicted dropout rate is approximately 15% at 1 year. This sample size is also based on a planned non-binding Interim analysis that will be conducted when 60% of the PFS events are observed, by using Lan-DeMets alpha spending function (see Section 9.4.5). In addition, contingent upon

rejection of the null hypothesis for the PFS endpoint, this sample size allows to apply the log-rank test to have an overall 1-sided significance level of 0.1 and power of 0.63 to demonstrate improvement of OS after 50 deaths are observed, assuming improvement in median OS from 8.5 months to 13.5 months and an HR=0.63.

9.4. Efficacy Analysis

9.4.1. Analysis of Progression-Free Survival (PFS)

PFS is defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause, whichever occurs first. PFS data will be censored on the day following the date of the last on treatment (including 28 day follow-up period after last dose) tumor assessment documenting absence of progressive disease for patients who do not have objective tumor progression and who do not die due to any cause while on treatment or who are given antitumor treatment other than the study treatment prior to observing objective tumor progression. Patients lacking an evaluation of tumor response after randomization will have their event time censored on the date of randomization with duration of 1 day. PFS will be compared between the 2 treatment arms using a one-sided log-rank test with a significance level of 0.1 (alpha=0.2). Cox proportional hazard models will be used to calculate the HR and to explore the potential influences of the baseline factors (eg, age, gender and ethnic origin) on PFS. The PFS probability at 1 year will be estimated for each treatment arm using the Kaplan-Meier method and the 2-sided 80% and 90% confidence interval for the log [-log(1-year PFS probability)] will be calculated using a normal approximation and then back transformed to give the confidence interval for the 1-year PFS rate itself. Analyses of PFS will be conducted when n=57 PFS events are observed. An Interim Analysis (IA) will be conducted based on PFS after 34 patients have had an event, which is 60% of the total required number of events (ie, 57 events). Efficacy, in terms of PFS, would be declared at the time of the IA if the HR surpasses the IA boundary for efficacy that is HR≤0.533. Futility, in terms of PFS, would be declared at the time of IA if the HR surpasses the IA boundary for futility that is HR >0.863.

9.4.2. Analysis of Objective Overall Response (ORR: CR or PR)

ORR is defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST, relative to all randomized patients who have baseline measurable disease. Confirmed responses are those that persist on repeat imaging study ≥4 weeks after initial documentation of response. Patients who do not have on-study radiographic tumor re-evaluation or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR. A patient, who initially meets the criteria for a PR and then subsequently becomes a confirmed CR, will be assigned a best response of CR.

ORR, CR and PR point estimates for each treatment arm will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method.[44] The difference between the two treatments in Phase 2 will be estimated and the corresponding 80% and 95% confidence intervals will be constructed using an exact method.[45]

9.4.3. Analysis of Duration of Objective Response (DR).

DR is defined as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. DR data will be censored on the day following the date of the last on treatment (including 28 day follow-up period after last dose) tumor assessment documenting absence of progressive disease for patients who do not have objective tumor progression and who do not die due to any cause while on treatment or who are given antitumor treatment other than the study treatment prior to observing objective tumor progression. Patients who achieve a PR and then a CR will have times calculated using the date of the PR as the first day. DR will only be calculated for the subgroup of patients with objective response.

Estimates of the DR curves from the Kaplan-Meier method will be presented. This method will be applied to derive the median event time and a confidence interval for the median for each treatment arm.

9.4.4. Analysis of Overall Survival (OS)

OS is defined as the time from date of randomization to date of death due to any cause. For patients not expiring, their survival times will be censored at the last date they are known to be alive. Patients lacking data beyond the day of randomization will have their survival times censored at the date of randomization with duration of 1 day.

For the main analysis, OS in each arm will be assessed using the Kaplan-Meier method and treatment arms will be compared by using a log-rank test (alpha=0.2) in the intent-to-treat population. Although this study is not powered to detect significant differences in Overall Survival at the time of the primary analyses of PFS, analyses of OS (similarly to the analyses described in Section 9.4.1), with a statistical power = 63%, will be conducted after 50 deaths are observed, assuming an HR=0.63 and improvement in median OS from 8.5 months to 13.5 months. First type error will not be inflated as this statistical comparison will be conducted conditionally upon rejection of the null hypothesis for the PFS endpoint (see Section 9.4.1).

9.4.5. Statistical Methods for Interim Analysis

A non-binding Interim Analysis (IA) will be conducted based on PFS after 34 patients have had an event, which is 60% of the total required number of events (ie, 57 events). Efficacy, in terms of PFS, would be declared at the time of the IA if the HR surpasses the IA boundary for efficacy that is HR≤0.533. Futility, in terms of PFS, would be declared at the time of IA if the HR surpasses the IA boundary for futility that is HR>0.863. Lan-DeMets alpha spending function with the O'Brien-Fleming boundaries[46,47] was used to define both the boundaries for efficacy and futility. This function spends the type-1 error very sparingly in the beginning but rapidly increase the pace of spending as the trial nears completion.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of PF-04136309 Pharmacokinetics

The concentration-time data of PF-04136309 will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) according to dose level.

For patients enrolled in the Phase 1 dose finding cohorts, the concentration-time data of PF-04136309 within the 12-hour dose interval on Day 15 (with the pre-dose sample collected on Day 16 as the 12-hour post dose sample) will be analyzed for individual patients using non-compartmental methods. The noncompartmental analysis will estimate PK parameters including $C_{max,ss}$, T_{max}, $AUC_{tau,ss}$, $C_{min,ss}$, $CL_{ss/F}$, and as data permit, $t_{1/2}$ and $V_{ss/F}$. The PK parameters will be summarized using descriptive statistics according to dosing cohort.

The concentration-time data of PF-04136309 from all patients enrolled in the study will be using nonlinear mixed effect modeling. The modeling-based analysis will estimate the typical value and variability for PK parameters including oral clearance (CL/F) and apparent volume of distribution (V/F). Also, the influence of selected potential covariates on the PK parameters will be explored as appropriate; the potential covariates to be explored will include selected demographics (eg, body weight, age, sex) and selected patient characteristics (eg, baseline CCR2 expression, baseline CCL2 level, ECOG performance status, liver function markers).

Population PK assessment will be conducted with the concentration-time data of PF-04136309 from all patients, using the nonlinear mixed effect modeling approach in accordance with regulatory guidances. A structural PK model based on data from the Phase 1b portion will be used. The population PK analysis will estimate typical value and variability for PK parameters including oral clearance (CL/F) and apparent volume of distribution (Vd/F). Also, the influence of selected potential covariates on the PK parameters will be explored as appropriate; the potential covariates to be explored will include selected demographics (eg, body weight, age, sex) and selected patient characteristics (eg, baseline CCR2 expression, baseline CCL2 level, ECOG performance status, liver function markers).

The detailed procedures for the population PK analysis, including the model implementation and evaluation, will be described prospectively in the Population Modeling Analysis Plan (PMAP). The results of the analysis will be summarized in a Population Modeling and Analysis Report (PMAR), separate from the clinical study report.

9.5.2. Analysis of Pharmacodynamics

For FNA and core-biopsy samples, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and post-treatment. For each pair of specimens, the percent change from baseline of these same parameters will also be calculated.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA). The statistical approach will examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor/anti-cancer efficacy.

The percentage change from baseline for pharmacodynamics biomarkers over the period of the study will be tabulated by individual. The mean change from baseline values over time per cohort will also be tabulated. Data will be presented in tabular and/or graphical format and summarized descriptively. Changes from baseline in biomarker readouts will be correlated with pharmacokinetic and clinical measures, as appropriate. Pharmacodynamic biomarkers submitted to these analyses may include, but not be limited to:

- Proportions of IM, TAM and other immune cell type of interest in peripheral blood, bone marrow and paired tumor biopsy.
- CCL2 levels in the peripheral blood.
- Relative expression of immune-related transcripts in tumor tissue and peripheral blood.
- Expression level of tumor biomarkers including but not limited to CA 19.9.

9.5.3. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-04136309 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.6. Safety Analysis

Adverse events, ECGs, blood pressure, pulse rate, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurologic examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurologic examinations conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set.

9.6.1. Analysis of the Primary Endpoint

Phase 1b: Dose-Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD and RP2D as described in the STUDY DESIGN section. Adverse Events constituting DLTs will be listed per dose level.

Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

Phase 2: PFS is the primary endpoint (see Section 9.4.1).

9.6.2. Analysis of Secondary Safety Endpoints

9.6.2.1. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline (Screening) and on-treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, response rate (RR), PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate), and by study arm and dose. Individual QT` (all evaluated corrections) intervals will be listed by study arm time and dose. The most

appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by study arm dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction method will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %)). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.6.2.2. Analyses of Peripheral Neurological Adverse Events, EORTC QLQ-C30 and QLQ-CIPN20 Questionnaires

Summary statistics, including frequencies, means, medians, range will be conducted. Times to neurotoxic events will be calculated, and Kaplan- Meier techniques will be employed to evaluate differences in treatment arms. Multi-variate analysis to adjust for some parameters may be conducted, if deemed appropriate.

Response to all questions of EORTC QLQ-30 and QLQ-CIPN20 questionnaires will be shown in percentage. Logistic regression analyses may be conducted at each visit to detect potential differences regarding neuropathy problems at the corresponding visit (EORTC QLQ-CIPN20 or QLQ-30 (except the last two questions on global health status); answer categories “quite a bit” or “very much” combined) between the two treatments in Phase 2.

Summary statistics will be provided by treatment for the raw scores of functional, Symptom and global health status raw subscales in QLQ-C30 as well as for linearly converted scores on the scale of 0-100 for these subscales. Summary statistics will also be provided for the raw scores of sensory, motor and automic scales raw subscales in QLQ-CIPN20 as well as for linearly converted scores on the scale of 0-100 for these subscales. Analysis of covariance (ANCOVA) models which include covariates of treatment and baseline may be employed to compare the two treatments by visit in each of the three-category scales of QOL-C30 and each of the three-category scales of QLQ-CIPN20.

Details of analyses of peripheral neurological adverse events, EORTC QLQ-C30 and QLQ-CIPN20 questionnaire will be provided in the SAP.

9.7. Analysis of Other Endpoints

Analyses of ORR, DR, OS and other Pharmacokinetics and Pharmacodynamics endpoints are described in Section 9.4.2, 9.4.4 and 9.5 respectively.

9.8. Data Safety Monitoring Committee

For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

Surveillance for serious adverse events (SAEs) according to regulatory guidelines;

Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level is an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

An external Data Monitoring Committee (DMC) will be established for the Phase 2 portion study. The external DMC will evaluate efficacy and safety data and make a recommendation about early termination due to observed results of the study.

9.9. Interim Analysis

Phase 1/b: This is a sponsor-open study. The Sponsor will conduct reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or to support clinical development.

Phase 2: The Phase 2 portion of the study is a double-blind randomized, multi-center, comparative safety and efficacy assessment of PF-04136309 in combination with nab-paclitaxel + gemcitabine versus SOC: nab-paclitaxel + gemcitabine + placebo in patients with mPDA.

Safety: An external DMC will monitor the safety of the patients on a periodic basis. The DMC will determine whether the trial should be terminated based on ongoing reviews of safety data.

Efficacy: The external DMC will also evaluate efficacy data and make a recommendation about early termination due to observed results of the study (see Section 9.4.5). Unblinded results will be reviewed by a designated limited number of experts. Refer to the study's Data Blinding Plan and/or Statistical Analysis Plan for specific details including delineation of members who will be involved in these unblinded reviews as well as steps to be instituted ahead of initiation of any unblinded review to ensure study integrity is maintained.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH) guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board /Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient when applicable, before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. All advertisements must be approved by the study Sponsor prior to use.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Participating Countries

End of trial in all participating countries is defined as the time at which all patients enrolled in the study have completed the last study visit and data from those visits have been reviewed by the investigator or designee.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-04136309 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within one week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

16. REFERENCES

1. Rodríguez D, Silvera R, Carrio R, et al. Tumor microenvironment profoundly modifies functional status of macrophages: peritoneal and tumor-associated macrophages are two very different subpopulations. Cell Immunol. 2013 May-Jun;283(1-2):51-60.

2. Rolinski J & Hus I. Breaking immunotolerance of tumors: a new perspective for dendritic cell therapy. J Immunotoxicol. 2014 Oct;11(4):311-8.

3. Markowitz J, Brooks TR, Duggan MC, et al. Patients with pancreatic adenocarcinoma exhibit elevated levels of myeloid-derived suppressor cells upon progression of disease. Cancer Immunol Immunother 2015; 64(2):149-59.

4. Karakhanova S, Link J, Heinrich M, et al. Characterization of myeloid leukocytes and soluble mediators in pancreatic cancer: importance of myeloid-derived suppressor cells. Oncoimmunology. 2015 Jan 22;4(4):

5. Sanford DE, Belt BA, Panni RZ, et al. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. Clin Cancer Res 2013; 19(13):3404-15.

6. Diaz-Montero CM, Salem ML, Nishimura MI, et al. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother 2009; 58(1):49-59.

7. Yang L, DeBusk LM, Fukuda K, et al. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell 2004; 6(4):409-21.

8. Bunt SK, Yang L, Sinha P, et al. Reduced inflammation in the tumor microenvironment delays the accumulation of myeloid-derived suppressor cells and limits tumor progression. Cancer Res 2007; 67(20):10019-26.

9. Melani C, Sangaletti S, Barazzetta FM, et al. Amino-bisphosphonate-mediated MMP-9 inhibition breaks the tumor-bone marrow axis responsible for myeloid-derived suppressor cell expansion and macrophage infiltration in tumor stroma. Cancer Res 2007; 67(23):11438-46.

10. Zhang B, Zhang Y, Bowerman NA, et al. Equilibrium between host and cancer caused by effector T cells killing tumor stroma. Cancer Res 2008; 68(5):1563-71.

11. Sinha P, Clements VK, Bunt SK, et al. Cross-talk between myeloid-derived suppressor cells and macrophages subverts tumor immunity toward a type 2 response. J Immunol 2007; 179(2):977-83.

12. Srivastava MK, Sinha P, Clements VK, et al. Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. Cancer Res 2010; 70(1):68-77.

13. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009; 9(3):162-74.

14. Marx J. Cancer immunology. Cancer's bulwark against immune attack: MDS cells. Science 2008; 319(5860):154-6.

15. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J. Immunol. 2009; 182(8):4499-506.

16. Ostrand-Rosenberg S. Myeloid-derived suppressor cells: more mechanisms for inhibiting antitumor immunity. Cancer Immunol Immunother 2010; 59(10):1593-600.

17. Huang B, Lei Z, Zhao J, et al. CCL2/CCR2 pathway mediates recruitment of myeloid suppressor cells to cancers. Cancer Lett 2007; 252(1):86-92.

18. Huang B, Pan PY, Li Q, et al. Gr-1+CD115+ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host. Cancer Res 2006; 66(2):1123-31.

19. Koga M, Kai H, Egami K, et al. Mutant MCP-1 therapy inhibits tumor angiogenesis and growth of malignant melanoma in mice. Biochem Biophys Res Commun 2008; 365(2):279-84.

20. White FA, Feldman P, Miller RJ. Chemokine signaling and the management of neuropathic pain. Mol Interv 2009; 9(4):188-95.

21. Pevida M, Lastra A, Hidalgo A, et al. Spinal CCL2 and microglial activation are involved in paclitaxel-evoked cold hyperalgesia. Brain Res Bull 2013; 95:21-7.

22. Zhang H, Boyette-Davis JA, Kosturakis AK, et al. Induction of monocyte chemoattractant protein-1 (MCP-1) and its receptor CCR2 in primary sensory neurons contributes to paclitaxel-induced peripheral neuropathy. J Pain 2013; 14(10):1031-44.

23. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. Eur J Cancer 2005; 41(8):1135-9.

24. Lavoie Smith EM, Barton DL, Qin R, et al. Assessing patient-reported peripheral neuropathy: the reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20 Questionnaire. Qual Life Res 2013; 22(10):2787-99.

25. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium and Magnesium to Prevent Oxaliplatin-Induced Sensory Neurotoxicity (N08CB/Alliance). J Clin Oncol 2014; 32(10):997-1005.

26. Pachman DR, Qin R, Seisler DK, et al. Clinical Course of Oxaliplatin-Induced Neuropathy: Results From the Randomized Phase III Trial N08CB (Alliance). J Clin Oncol 2015; 33(30):3416-22.

27. Leal AD, Qin R, Atherton PJ, et al. North Central Cancer Treatment Group/Alliance Trial N08CA-The Use of Glutathione for Prevention of Paclitaxel/Carboplatin-Induced Peripheral Neuropathy. Cancer 2014; 120(12):1890-7.

28. Puttabasavaiah S, Heshan L, Qin R, et al. A comparison of simple single-item measures and the NCI Common Toxicity Criteria version 3.0 measure of peripheral neuropathy. J Clin Oncol 2012; 30(Suppl 15):Abstr 1557.

29. Mitchem JB, Brennan DJ, Knolhoff BL et al. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res. 2013 Feb 1;73(3):1128-41.

30. Chanmee T, Ontong P, Konno K, Itano N Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel). 2014 Aug 13;6(3):1670-90.

31. Mantovani A, Sica A. Macrophages, innate immunity and cancer: balance, tolerance, and diversity. Curr Opin Immunol. 2010 Apr;22(2):231-7.

32. Franklin RA, Liao W, Sarkar A, The cellular and molecular origin of tumor-associated macrophages. Science. 2014;344(6186):921-5.

33. Chanmee T, Ontong P, Konno K, Itano N Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel). 2014 Aug 13;6(3):1670-90.

34. Mantovani A, Sica A. Macrophages, innate immunity and cancer: balance, tolerance, and diversity. Curr Opin Immunol. 2010 Apr;22(2):231-7.

35. Y Ji, P Liu, Y Li, and BN Bekele. A modified toxicity probability interval method for dose-finding trials. Clinical Trials 2010;7:653-66.

36. M. Fanale, L. Fayad, B. Pro, F. Samaniego, M. Liboon, C. Nunez, S. Horowitz, P. Anderlini, U. Popat, Y. Ji, LW. Kwak, and A. Younes. Phase I study of bortezomib plus ICE (BICE) for the treatment of relapsed/refractory Hodgkin lymphoma. British Journal of Haematology 2011;154:284-286.

37. Dykstra R, Robertson T. An algorithm for isotonic regression for two or more independent variables. Ann Stat. 1982;10:708-716.

38. Bonapace L, Coissieux MM, Wyckoff J, et al. Cessation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis. Nature 2014; 515(7525):130-3.

39. Wang-Gillam, et al. Phase 1b study of FOLFIRINOX plus PF-04136309 in patients with borderline resectable and locally advanced pancreatic adenocarcinoma(PC). J Clin Oncol 2015; 3(Suppl):Abstr 338.

40. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival on pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691-703.

41. "Metabolism and Transport, Drug Interaction Database," Department of Pharmaceutics, University of Washington. www.druginteractioninfo.org. Accessed May 2009.

42. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. JCO Jul 1, 2006:3187-3205.

43. Ji Y & Wang SJ. Modified toxicity probability interval design: A safer and more reliable method than the 3+3 design for practical Phase 1 trials. J Clin. Onc. 2013;31:1-12.

44. Blyth, C. R. and Still, H. A. (1983). Binomial Confidence Intervals. Journal of the American Statistical Association 78, 108–116.

45. Chan, I. S. F. and Zhang, Z. (1999), "Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions," Biometrics, 55, 1202–1209.

46. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med 1994; 13(13-14):1341-52; discussion 1353-6.

47. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70:659-63.

Appendix 1. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Note: For the patient population being evaluated in this protocol, the baseline assessment may be completed within 6 weeks prior to randomization.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

    - one or more target measurable lesions have not been assessed;

    - or assessment methods used were inconsistent with those used at baseline;

    - or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

    - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

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

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 1. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Appendix 2. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 4.03 date June 14, 2010) has been placed in the Study Manual for this protocol. Alternatively, the NCI CTCAE may be reviewed on-line at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html

Appendix 3. ECOG Performance Status

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

*As published in Am J Clin Oncol 5:649-655, 1982.

Appendix 4. Sample Patient Study Drug Log

Complete this Patient Study Drug Log to ensure all doses are accounted for.

Patient Number: _____ - _____

Date (DD/MMM/YYYY)	Dose		Reasons for missed doses, description of any symptoms, or other.
	Morning (AM)	Night (PM)	

Appendix 5. Neurotoxicity Examination

Patient Name: _____
Chart Number: _____
Patient ID: _____

Pfizer A9421018

NEUROTOXICITY EVALUATION (NCI – CTCAE version 4.0)

O Not Done

Date of Evaluation
(dd-MMM-yyyy): _____

		GRADE 0	GRADE I	GRADE II	GRADE III	GRADE IV
1.	Do you have problems tying shoe laces, buttoning your shirts, fastening buckles or pulling up zippers?	O	O	O	O	O
2.	Do you have problems writing?	O	O	O	O	O
3.	Do you have problems putting on your jewelry or your watch?	O	O	O	O	O
4.	Do you have problems walking?	O	O	O	O	O

Comments: _____

_____

MD Signature: _____ **Date:** _____

(or medically qualified delegate)

A9421018 v2.0 dated 26-Aug-16

Appendix 6. EORTC Quality of Life Questionnaire C30

ENGLISH

EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 7. EORTC Quality of Life Questionnaire CIPN20

ENGLISH

EORTC QLQ – CIPN20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	Not at All	A Little	Quite a Bit	Very Much
31 Did you have tingling fingers or hands?	1	2	3	4
32 Did you have tingling toes or feet?	1	2	3	4
33 Did you have numbness in your fingers or hands?	1	2	3	4
34 Did you have numbness in your toes or feet?	1	2	3	4
35 Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36 Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37 Did you have cramps in your hands?	1	2	3	4
38 Did you have cramps in your feet?	1	2	3	4
39 Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
40 Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
41 Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
42 Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
43 Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
44 Did you have difficulty walking because your feet dropped downwards?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week :	Not at All	A Little	Quite a Bit	Very Much
45 Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
46 Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
47 Did you have blurred vision?	1	2	3	4
48 Did you have difficulty hearing?	1	2	3	4
Please answer the following question only if you drive a car				
49 Did you have difficulty using the pedals?	1	2	3	4
Please answer the following question only if you are a man				
50 Did you have difficulty getting or maintaining an erection?	1	2	3	4