A PHASE 1B OPEN-LABEL THREE-ARM MULTI-CENTER STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF PF-05212384 (PI3K/MTOR INHIBITOR) IN COMBINATION WITH OTHER ANTI-TUMOR AGENTS

Compound:	PF-05212384 (gedatolisib); PF-00299804
Compound Name:	Gedatolisib; Dacomitinib
US IND Number:	[redacted]
European Clinical Trial Database (EudraCT) Number:	2013-001390-24
Protocol Number:	B2151002
Phase:	1b

Document History

Document	Version Date	Summary of Changes
Amendment 5	11 November 2016	The purpose of the amendment was to: Include rationale and description of a two arm expansion in patients with PF-05212384 in combination with cisplatin in adult woman with metastatic or locally-recurrent/advanced triple hormone-receptor negative breast cancer (TNBC) in first- through third-lines of therapy. Add collection of Patient Reported Outcome (PRO) questionnaires for patients enrolled in the expansion. Add collection of Circulating Tumor Cells at screening for patients enrolled in the expansion. Administrative, editorial and typographical updates were made.
Amendment 4	15 July 2015	The purpose of the amendment was to: Include reference to the generic name for PF-05212384 in the header and protocol title page. Protocol Summary, Study Design, Section 3. Study Design and Section 9.3 Sample Size Determination: • Modify language due to typographical errors that were made when protocol Amendment 3 was implemented. • Add language regarding the Pfizer decision on April 1, 2015 to stop enrolment in Arms A and C of the B2151002 clinical trial. The decision is based on the company's change in prioritization for the portfolio and is not due to any safety concerns or regulatory interactions. Schedule of Activities, Footnote 17

		• Modify tumor assessment schedule for patients that remain on study for >12 cycles from every 6 weeks (±5 days) to every 9 weeks (±5 days) to decrease the burden on the patients and sites while still ensuring adequate monitoring for safety and efficacy. Schedule of Activities, Footnote 23 • Additional language to clarify that collection of archival tissue post announcement of Pfizer's decision to close Arm A and C is at the discretion of the investigator. In addition, in the event archival tissue is not available, a fresh biopsy is no longer required. Section 4.1 Inclusion Criteria, #4 and Section 6.1. Screening • Added reference to Footnote 23 regarding collection of archival tissue. • Specify that ovarian cancer (OC) patients can be enrolled in Arm B as cisplatin is indicated in OC patients. Section 4.2. Exclusion Criteria, #8 and Section 5.4.1 Drugs Interacting with CYP3A4 • Removed aprepitant from list of exclusionary medications at study entry and on study. The use of "aprepitant" is classified as a moderate CYP3A4 inhibitor and is permitted in the event that an alternative anti-emetic cannot be utilized. Section 4.3. Life Style Guidelines • An administrative clarification to include the investigator's designee per Pfizer's modified protocol template language. Section 5.2.3.1 PF-05212384

		• Added language to allow for the possibility that an infusion could exceed the protocol defined 30 minutes. This is permitted in the event of allergic/infusion reactions, and investigators should institute treatment measures according to best medical and nursing practice and the infusion time can be extended to a maximum of 60 minutes. Section 5.2.4 Medication Errors • Updates made per Pfizer protocol template updates. Section 8 Adverse Event Reporting • Updates made per Pfizer protocol template updates. Section 9.1 Analysis Sets • Text was added to describe how PK samples will be handled when the infusion time exceeds the planned 30 minute infusion time. This text is necessary since the protocol will allow for the infusion to be extended in the event of an infusion related reaction. Section 15.1 Publication of Study Results • Updates made per Pfizer protocol template updates. Appendix 9. Management of Allergic Reactions or Anaphylaxis. • An appendix was added to provide further guidance on management of infusion related reactions.
Amendment 3	27 May 2014	The purpose of the amendment was to: • Include additional dose levels to be tested in each study Arm.

		• Patients who are tolerating treatment at the lower dose levels to escalate to the next highest dose at which safety/tolerability has already been established in the study. • Clarifications were made to pharmacokinetic sampling and treatment tables to include dosing after Cycle 7. • Clarifications were made to eligibility criteria with respect to QT/QTc prolongation. • Modifications were made to the Sample size for each arm due to the addition of dose levels.
Amendment 2	07 October 2013	The primary purpose of the amendment is to incorporate feedback based on Health Authority feedback. In addition, modifications were made to allow for the use of luteinizing-hormone-releasing hormone and low dose steroids for patients that have castrate resistance prostate cancer in Arm A and clarifications were made to several exclusion criteria.
Amendment 1	10 June 2013	• Revise US IND Number. • Remove PK sample collected at Baseline. • Add two additional ECG collection timepoints in Arms A and B to better match the schedule with Arm C. • Administrative Changes.
Original protocol	27 March 2013	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review board (IRB)/external review board (ERB), etc.

PROTOCOL SUMMARY

Rationale:

Signaling through the (phosphatidylinositol 3-kinase) PI3K pathway is associated with resistance to a variety of anti-tumor agents. This has been described pre-clinically with cytotoxic chemotherapeutic agents with varying mechanisms of action including taxanes, and (deoxyribonucleic acid) DNA-damaging agents. In the clinic, activated PI3K pathway in tumors has been correlated with decreased response to therapy and worse clinical outcomes.

In addition to resistance to cytotoxic agents, there is also evidence of PI3K signaling affecting sensitivity of cells to epidermal growth factor receptor (EGFR) family signaling inhibitors. Specifically, the activation of PI3K in tumors has been associated with a worse outcome in patients with HER2-positive gastric cancer treated with anti-HER2 agents. In addition, pre-clinical studies have described the role of the PI3K pathway in EGFR activation in glioblastoma multiforme (GBM) and non-small cell lung cancer (NSCLC) cells and have demonstrated that PI3K inhibitors can reverse resistance to EGFR inhibitors in tumor models.

Collectively, these findings suggest that PI3K/mammalian target of rapamycin (mTOR) inhibitors may increase the efficacy of both chemotherapeutic agents which are considered standard of care (SOC) for the treatment of several solid tumors and dacomitinib which has shown clinical activity in several tumor types.

Objectives: Original Protocol through Amendment 4

Primary Objective

- To assess the safety and tolerability and to estimate the maximum tolerated dose (MTD) of the following combinations in patients with advanced solid tumors:
    - Arm A: PF-05212384 and docetaxel.
    - Arm B: PF-05212384 and cisplatin.
    - Arm C: PF-05212384 and dacomitinib.

Secondary Objectives

- To evaluate the overall safety profile.
- To assess the effects of PF-05212384 on the pharmacokinetics (PK) of docetaxel, cisplatin and dacomitinib and *vice versa* in Arms A, B, and C respectively.
- To evaluate possible biomarkers of efficacy (eg, *KRAS* mutation) and pharmacodynamic (PD) effects in paired tumor biopsies (eg, pAkt levels) and serum (eg, insulin levels).

- To characterize the effects of the combinations on the potential to prolong the QTc interval.

- To document anti-tumor activity.

Endpoints: Original Protocol through Amendment 4

Primary Endpoint

- Dose Limiting Toxicity (DLT).

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03), timing, seriousness and relationship to study therapy.

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

- Vital sign abnormalities.

- Single and multiple dose pharmacokinetic (PK) parameters of PF-05212384, and other anti-tumor agents (docetaxel, cisplatin or dacomitinib) alone and together, respectively.

- Gene sequence data (eg, *PIK3CA*, *KRAS)* and levels of PI3K pathway protein biomarkers (eg, pAkt, PTEN, circulating insulin).

- QTc interval.

- Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.

Objectives - Safety and Efficacy Expansion in Patients with Triple Negative Breast Cancer (TNBC)

Primary Objective

- To evaluate the anti-tumor activity of PF-05212384 plus cisplatin in patients with TNBC.

Secondary Objectives

- To continue to evaluate the overall safety profile of the combination of PF-05212384 plus cisplatin.

- To characterize single and multiple dose pharmacokinetics following intravenous (IV) administration of PF-05212384.
- To characterize the effects of the combinations on the potential to prolong the QTc interval.
- To evaluate additional anti-tumor activity.
- To assess patient reported outcomes (PRO) of global quality of life (QOL) and disease/treatment-related symptoms of advanced breast cancer.

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- [redacted]

Endpoints - Safety and Efficacy Expansion in patients with TNBC.

Primary Endpoint

- Objective response (OR) as assessed by the Investigator using RECIST version 1.1.

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.
- Single and multiple dose PK parameters of PF-05212384.
- QTc interval.
- Clinical Benefit Response (CBR), Duration of Response (DR) and Progression Free Survival (PFS) (as assessed using RECIST version 1.1).
- Time to deterioration in global QOL.
- Change from baseline in global QOL and disease/treatment-related symptoms.

CCI [redacted]

- [redacted]

Study Design:

This is a Phase 1b, three-arm, open-label, multi-center, multiple dose, dose escalation, safety, tolerability, pharmacokinetic and pharmacodynamic study of PF-05212384 in combination with anti-tumor agents in sequential cohorts of adult patients with select advanced solid tumors. Successive cohorts of patients will receive selected doses of PF-05212384 in combination with selected doses of chemotherapeutic agents (docetaxel and cisplatin) or dacomitinib in 3 independent arms on an outpatient basis. Based on the tolerability of PF-05212384 at higher doses in other (monotherapy) studies, the study will test increasing doses of PF-05212384 in combination with docetaxel, cisplatin, and/or dacomitinib in order to select the best dose to administer in the MTD expansion portion of the study.

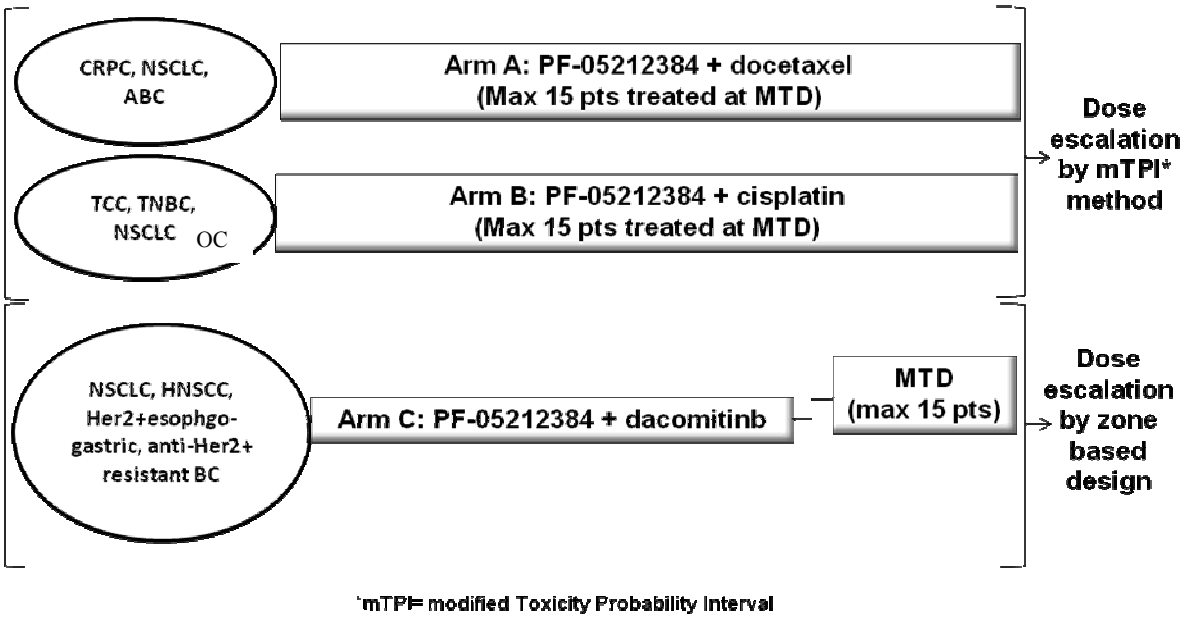
A modified toxicity probability interval (mTPI) method with adjustment based on observed DLT rate will be used to guide the dose assignment in Arms A and B. The actual dose selected for the next cohort will take into account the recommended dose by using the adjusted mTPI method as well as safety data other than DLTs. In Arm C in order to evaluate concurrent doses of dacomitinib in combination with two concurrent doses of PF-05212384, a zone-based design will be utilized, which is a modified 3+3 design that potentially allows opening of more than one dose level at the same time.[35] In all arms, dose escalation will proceed until an MTD (or two MTDs) is declared, or the Maximum Allowable Dose is reached.

On April 1, 2015, Pfizer Inc. has decided to stop enrolment in Arms A and C of the B2151002 clinical trial. Patients previously identified for enrolment in Arm A and C were permitted to enter the study after notification of the decision. Due to closure, the MTD of those combinations will not be established. All references to objectives, endpoints, study design, assessments, etc. and analysis of data in Arm A and C will be limited to the number of patients treated up to the enrolment discontinuation date for each Arm (June 10, 2015 for Arm A and 06 July 2015 for Arm C). The decision is based on the company's change in prioritization for the portfolio and is not due to any safety/efficacy concerns or regulatory interactions.

For Arm B, the study was originally designed as a dose escalation study with no expansion cohorts. However, Protocol Amendment 5 includes the rationale and description for the safety and efficacy expansion with PF-05212384 plus cisplatin in patients with metastatic or locally-recurrent/advanced TNBC. A total of 21 patients were enrolled in Arm A, 33 in Arm B and 33 patients in Arm C. Approximately 124 patients are expected overall including the safety and efficacy expansion. Pharmacodynamic studies will be performed in paired tumor biopsies, when clinically feasible, to evaluate PI3K and mTOR pathway inhibition at the PF-05212384 doses used in the MTD. Paired biopsies that are obtained during dose escalation and expansion will also be evaluated for modulation of PI3K signaling.

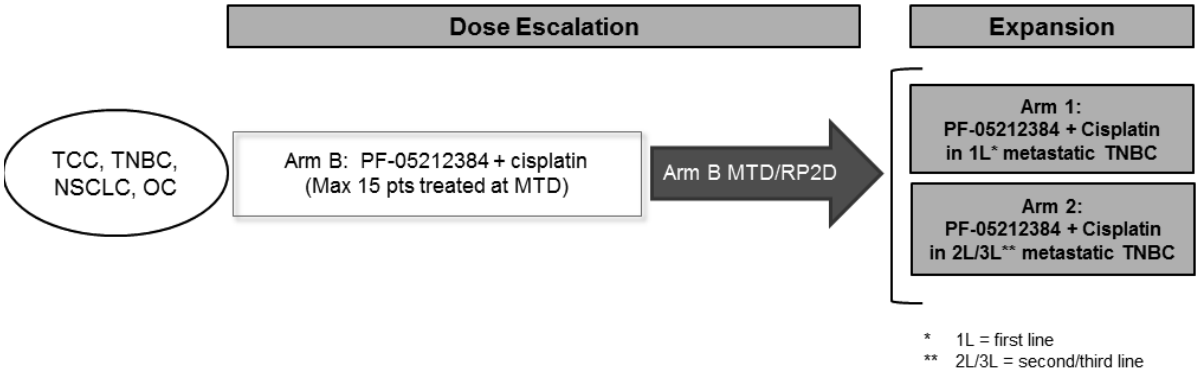
Each of the treatment arms are restricted to patients with tumor types for which the combination partner is either considered standard-of-care, or in the case of dacomitinib, are indications which have been shown to be sensitive.

Figure 1. Original Overall Study Design



CRPC: Castrate resistant prostate cancer; NSCLC: Non-small cell lung cancer; ABC: Advanced breast cancer; TCC: Transitional cell cancer; TNBC: Triple negative breast cancer; OC: ovarian cancer; HNSCC: Head and neck squamous cell cancer; BC: Breast cancer

Figure 2. Amendment 5 Study Design



To understand the single-dose safety and single dose PK of the study drug, a lead in period will be included. A single lead-in dose of PF-05212384 will be given either 7 days prior to Cycle 1 Day 1 (Arms A and B) or 14 days prior to Cycle 1 Day 1 (Arm C). The lead in period duration, subsequent doses, regimens and PK time-points may be modified based on the PK profile observed during the lead in period. Patients will then receive study treatment on an outpatient basis as 21 day cycles.

Treatment with study drug will continue until progression of disease, uncontrollable toxicity, a decision by the patient or Investigator to discontinue treatment, or the study is terminated. Patients experiencing toxicity may be managed with dose modification or discontinuation. If a patient discontinues PF-05212384 or the combination partner (cisplatin, docetaxel or dacomitinib) due to toxicity which is specific to either agent, continuation of patient treatment within the study with single agent PF-05212384, cisplatin, docetaxel, or dacomitinib will be discussed with the Sponsor on a case-by-case basis.

Statistical Method:

The MTD estimation in Arms A and B employs the mTPI method with adjustment of dose assignment criteria based on observed DLT rate. The mTPI method is a Bayesian method with only one assumption about the dose-toxicity relationship, which is, toxicity increases as dose increases. For Arm C, a zone-based design will be employed for MTD estimation. This is a 3+3 design modified for 2-dimensional MTD finding. The expansion portion of the study with cisplatin in combination with PF-05212384 in patients with metastatic or locally-recurrent TNBC will assess safety and efficacy in 2 separate groups of 15 patients, for a total of at least 30 patients.

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.

Arms A and B (Original Protocol through Amendment 4)

Protocol Activity			Cycle 1				Cycle 2 and beyond			End of Treatment[26]	Follow Up[27]
	Screen/ Baseline[1]	7 Days prior to C1D1	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15		
Visit Window		**±1 day**			**±1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**	**+7 days**	
Informed consent[2]	X										
Tumor history[3]	X										
Medical history[4]	X										
Baseline signs and symptoms[5]	X										
Physical examination[6]	X	X								X	X
Abbreviated physical examination[6]			X				X				
Weight	X		X				X			X	
Vital signs[7]	X	X	X				X			X	X
Performance status[8]	X	X	X							X	X
Laboratory[9] and other Safety Assessments											
Hematology[10]	X	X	X		X	X	X		X (Cycle 2 only)	X	
Blood chemistry[11]	X	X	X		X	X	X		X (Cycle 2 only)	X	
Coagulation[12]	X	X	X				X			X	
Urinalysis[13]	X	X	X				X			X	
Pregnancy test[14]	X	X					X			X	
ECG (12-lead)[15]	X			X			X (Cycle 2 only)				

Protocol Activity			Cycle 1				Cycle 2 and beyond			End of Treatment[26]	Follow Up[27]
	Screen/ Baseline[1]	7 Days prior to C1D1	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15		
Visit Window		±1 day			±1 day	±1 day	±2 days	±2 days	±2 days	+7 days	
Tumor Assessments											
CT/MRI scan [17]	X								X (every 6 weeks)	X	
Other Clinical Assessments											
Adverse events (AE) [18]	X	Continuous assessment and monitoring								X	X
Concomitant medications[19]	X	Continuous assessment and monitoring								X	X
Registration and Study Treatment[20]											
Registration[21]	X										
PF-05212384 IV[20]		Refer to Schedule of Study Treatment And Pharmacokinetic Assessments Table									
Docetaxel IV (Arm A only) [20]											
Cisplatin IV (Arm B only)[20]											
Pharmacokinetics and Pharmacodynamics											
Pharmacokinetics[22]		Refer to Schedule of Study Treatment And Pharmacokinetic Assessments Table									
Archival tumor biopsy for biomarker analysis[23]	X										
Paired tumor biopsies for pharmacodynamic biomarkers[24]	X							X		X	
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Safety laboratory tests (hematology, blood chemistry, urinalysis, coagulation) and tumor assessments may be done up to 72 hours prior to scheduled Day 1 visit on any cycle to facilitate availability of results to Investigator at the time of clinic visit. No time window is allowed for pregnancy test.

Arm C only (Original Protocol through Amendment 4)

Protocol Activity				Cycle 1				Cycle 2 and beyond			End of Treatment[26]	Follow Up[27]
	Screen/ Baseline[1]	14 Days prior to C1D1	7 Days prior to C1D1	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15		
Visit Window		±1 day	±1 day			±1 day	±1 day	±2 days	±2 days	±2 days	+7 days	
Informed consent[2]	X											
Tumor history[3]	X											
Medical history[4]	X											
Baseline signs and symptoms[5]	X											
Physical examination[6]	X	X									X	X
Abbreviated physical examination[6]				X				X				
Weight	X			X				X			X	
Vital signs[7]	X	X	X	X				X			X	X
Performance status[8]	X	X		X							X	X
Laboratory[9] and other Safety Assessments												
Hematology[10]	X	X		X		X	X	X		X (Cycle 2 only)	X	
Blood chemistry[11]	X	X		X		X	X	X		X (Cycle 2 only)	X	
Coagulation[12]	X	X		X				X			X	
Urinalysis[13]	X	X		X				X			X	
Pregnancy test[14]	X	X						X			X	
ECG (12-lead)[15]	X				X			X			X	
LVEF[16]	X									X (every 3/6 cycles)		
Tumor Assessments												
CT/MRI scan[17]	X									X (every 6 weeks)	X	
Other Clinical Assessments												
Adverse events (AE)[18]	X	Continuous assessment and monitoring									X	X
Concomitant medications[19]	X	Continuous assessment and monitoring									X	X

Protocol Activity				Cycle 1				Cycle 2 and beyond			End of Treatment[26]	Follow Up[27]
	Screen/ Baseline[1]	14 Days prior to C1D1	7 Days prior to C1D1	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15		
Visit Window		±1 day	±1 day			±1 day	±1 day	±2 days	±2 days	±2 days	+7 days	
Registration and Study Treatment[20]												
Registration[21]	X											
PF-05212384 IV[20]		Refer to Schedule of Study Treatment And Pharmacokinetic Assessments Table										
Dacomitinib PO (Arm C only) [20]												
Pharmacokinetics and Pharmacodynamics												
Pharmacokinetics[22]		Refer to Schedule of Study Treatment And Pharmacokinetic Assessments Table										
Archival tumor biopsy for biomarker analysis[23]	X											
Paired tumor biopsies for pharmacodynamic biomarkers[24]	X								X		X	
CCI												

Safety laboratory tests (hematology, blood chemistry, urinalysis, coagulation) and tumor assessments may be done up to 72 hours prior to scheduled Day 1 visit on any cycle to facilitate availability of results to Investigator at the time of clinic visit. No time window is allowed for pregnancy test.

Footnotes

1. **Screening/Baseline Assessments:** must be completed within 28 days prior to study treatment start unless otherwise specified as shown in the schedule of events above. Study treatment start is considered the lead-in dose; 7 days (Arms A and B) or 14 days (Arm C) prior to Cycle 1 Day 1.
2. **Informed Consent**: must be obtained prior to undergoing any study specific procedures.
3. **Tumor History:** will be collected within 28 days prior to first dose of study treatment. History of oncology disease will be collected including details of primary diagnosis and treatment history (surgery, systemic treatment and radiotherapy) as well as duration and best response to immediate prior regimen if available. When available, primary diagnosis history should include known molecular characteristics of the patient's tumor including mutations, amplifications, etc. (eg, EGFR mutation, HER2 expression, etc).
4. **Medical History:** will be collected within 28 days prior to first dose of study treatment. Includes history of disease process other than oncology (active or resolved) and concomitant illnesses. Includes prior treatment including dosing and duration of administration as well as verification of concurrent medication**.**
5. **Baseline Signs & Symptoms:** patients will be asked about any signs and symptoms experienced within the past 14 days of study treatment start. During study treatment, any new or worsened conditions since baseline will be reported on the Adverse Event CRF.

6. **Physical Exam:** will include an assessment for emergent toxicities or changes from prior visits. These procedures may be conducted by the Investigator or his/her designee. Abbreviated physical exams should be performed where a complete physical exam is not required, and on an as needed basis for assessment of adverse events. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.
7. **Vital signs:** will include height (baseline only), weight, blood pressure and heart rate to be recorded in the sitting position after approximately 5 minutes of rest.
8. **Performance status:** per ECOG scale to be assessed within 14 days prior to the first dose of study treatment, and as described in the table above (see Appendix 4).
9. **Laboratory Tests:** will be performed as indicated within 14 days prior to the first dose of study treatment and during treatment as described in the table above. Additional laboratory tests may be performed when medically indicated.
10. **Hematology:** to include platelet count, hemoglobin, and WBC count with 5- part differential. No need to repeat on day of first dose of study treatment if baseline assessment performed within 7 days.
11. **Blood Chemistry:** to include AST (SGOT), ALT (SGPT), serum creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase, chloride, uric acid, phosphorus, calcium, magnesium, potassium, sodium, BUN or urea, total protein, albumin, glucose (fasting), and insulin. HbA1c at screen/baseline, and then every other cycle or as indicated in the event of suspected hyperglycemia. No need to repeat on day of first dose of study treatment if baseline assessment performed within 72 hours. It is recommended that patients be under fasting conditions (no food or drink within 8 hours) for all blood chemistry panels on Day 1 of each cycle.
12. **Coagulation Tests:** to include partial thromboplastin time (PTT) and international normalized ratio (INR). No need to repeat on day of first dose of study treatment if baseline assessment performed within 72 hours.
13. **Urinalysis:** by dipstick is acceptable. Microscopic analyses if dipstick deemed abnormal per Investigator discretion. No need to repeat on day of first dose of study treatment if baseline assessment performed within 72 hours.
14. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once immediately before the lead-in dose. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.
15. **ECG:** Triplicate 12-lead ECG (per institutional practice) will be performed. At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval using Fredericia's correction formula. ECGs will be collected as follows:
    - Within 14 days prior to the first dose of study treatment;
    - Cycle 1 Day 2, immediately prior to completion of PF-05212384 infusion;
    - Cycle 2 Day 1, immediately prior to completion of PF-05212384 infusion;
    - Subsequent cycles on Day 1, immediately prior to completion of PF-05212384 infusion (Arm C only);
    - End of Treatment Visit (Arm C only).

The ECG should be collected prior to scheduled PK collections; the timing of the PK collections over rides the timing for ECG collections (ie, if a PK sample is scheduled at 1 hour post dose and an ECG is scheduled 1 hour post dose, then the ECGs should be collected just prior to the hour PK collection, and the PK sample should be collected at the nominal time). If the patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) an ECG should be obtained at time of the event. See Section 7 for additional considerations regarding ECG. If the mean QTc is prolonged (value of ≥500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs may be performed as clinically indicated.

16. **Left ventricular ejection fraction (LVEF) ARM C:** LVEF will be measured at baseline, the end of Cycle 3, end of Cycle 6, and then every 6 cycles for Arm C patients only. It will be measured by either echocardiogram (ECHO) or multi-gated radionucleide study (MUGA), with the same technique used throughout the study for an individual patient. If an absolute decrease in LVEF of greater than 20% is noted by either MUGA or ECHO, then the LVEF will be repeated as soon as feasible using the alternate radiologic method (if available); if the decrease is verified further, interruption of treatment for futher cardiac evaluation will be undertaken per the judgment of Investigator. In the absence of clinical signs and symptoms of left ventricular dysfunction or LVEF <40%, treatment may continue if judgment of the Investigator is that patient may benefit from ongoing therapy. For any patient discontinuing therapy for signs or symptoms suggestive of left ventricular dysfunction, continued evaluation of LVEF at about 3-4 month interval to assess for resolution is recommended.

17. **Tumor Assessments:** Tumor assessments will be performed every 6 weeks (±5 days) while the patient is receiving treatment regardless of treatment delays. Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans. A thoracic CT scan should be performed at every tumor assessment independent of lung involvement and in the absence of respiratory symptoms. Brain scans and bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out CNS metastases. Given the exploratory nature of the study, confirmation of response (CR/PR) is not required but can be collected. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. For those patients who discontinue for reasons other than progression of disease, tumor assessments should continue until progression of disease is documented. In patients continuing on study for >12 cycles and have experienced manageable toxicity and stable disease, the interval between imaging assessments may be modified from every 6 weeks (±5 days) to every 9 weeks (±5 days) if the Investigator determines it is in the best interest of the patient, and after discussion and approval by the Sponsor. The modification will decrease the burden on the patients and sites, while still ensuring adequate monitoring for safety and efficacy.

18. **Adverse Event (AE) Assessments:** AEs should be documented and recorded at each visit using NCI CTC AE version 4.03 (Appendix 3). Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy within that time frame. 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 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.

19. **Concomitant Medications:** All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases.

20. **Study Treatment:** Patients will be treated with PF-05212384 once weekly in 3 week cycles. Docetaxel and Cisplatin will be given once every 3 weeks. Dacomitinib will be taken daily. Details on study treatment are provided in the **Schedule of** STUDY TREATMENTS and Pharmacokinetics Assessments**.**

21. **Registration:** Patient enrollment number, treatment arm, and dose level allocation assigned by Pfizer Inc.

22. **PK Sampling:** Details on sampling are provided in the **Schedule of** STUDY TREATMENTS and Pharmacokinetics Assessments**.**

23. **Archival tumor biopsy for biomarker analysis:** All patients will be required to provide an archived tumor biopsy formalin fixed paraffin embedded (FFPE) sample. If an archived tumor sample is not available, patients must consent to provide a fresh biopsy FFPE for purpose of this analysis. Patients may not be enrolled into the study without providing either an archived or fresh tumor sample. For the tumor biopsy sample, paraffin blocks are preferred, but freshly cut slides are acceptable. Details for handling of these samples including processing, storage, and shipment will be provided in the Study Manual. Collection of archival tissue post announcement of Pfizer's decision to close Arm A and C is at the discretion of the investigator (in the event archival tissue is not available, a fresh biopsy is no longer required). The requirement for collection of archival tissue for patients enrolling in Arm B remains unchanged.

24. **Paired tumor biopsies for pharmacodynamic (PD) biomarkers** (see Section 7.3)**:** Fresh FFPE tumor biopsies will be requested at Screening (within 28 days of study treatment start) and on Cycle 2 Day 8 for all patients in both the dose escalation and the MTD cohorts in order to demonstrate pathway inhibition and for PD biomarker studies across doses. The paired tumor biopsy will be mandatory for patients enrolled in the MTD cohort unless it poses a safety risk to the patient in the opinion of the Investigator after discussion with the Sponsor. Tumor biopsies collected at End of Treatment are optional, but are highly desired, for a proteomics-based evaluation of possible resistance mechanisms to PI3K/Akt/mTOR axis therapies. Details for handling of these samples including processing, storage, and shipment will be provided in the Study Manual.

CCI [redacted]

26. **End of treatment visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).

27. **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, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment 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. For those patients who discontinue for reasons other than progression of disease, tumor assessments should continue until progression of disease is documented.

SCHEDULE OF STUDY TREATMENT AND PHARMACOKINETIC ASSESSMENTS ARM A (Original Protocol through Amendment 4)

			Cycle 1				Cycle 2			Cycle 3 - 6			Cycle 7 and Beyond		
Protocol Activity	**Screen/ Baseline**	**7 days prior to C1D1**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**
Study Treatment[1]															
PF-05212384		X		X	X	X	X	X	X	X	X	X	X	X	X
Docetaxel			X				X			X			X		
Pharmacokinetics															
PK for PF-05212384[2]		X					X			X					
PK for Docetaxel[3]			X				X								

1. **Study Treatment:** Arm A treatment with PF-05212384 will be initiated 7 days prior to Cycle 1 Day 1. On Cycle 1 Day 1 patients will receive docetaxel alone. On Cycle 1 Day 2, patients will receive treatment with PF-05212384 alone. On Day 1 for Cycles 2 and beyond, patients will receive docetaxel followed by PF-05212384.
2. **PK Sampling for PF-05212384:** Blood samples for pharmacokinetics will be taken at 0 hours (pre-dose), 0.5 hours (immediately after the infusion of PF-05212384), 1, 2, 4, 6, 24, 72, 96 and 168 hours post-dose 7 days prior to Cycle 1 Day 1 and on Cycle 2 Day 1. Pre-dose samples will be collected on Day 1 for Cycles 3-6.
3. **PK Sampling for Docetaxel:** Blood samples for pharmacokinetics will be taken at 0 hours (pre-dose), 1 hour (immediately after the infusion of Docetaxel) 1.5, 2, 4, 6, and 24 hours post-dose on Day 1 for Cycles 1 and 2.

SCHEDULE OF STUDY TREATMENT AND PHARMACOKINETIC ASSESSMENTS ARM B (Original Protocol through Amendment 4)

			Cycle 1				Cycle 2			Cycle 3 - 6			Cycle 7 and Beyond		
Protocol Activity	**Screen/ Baseline**	**7 days prior to C1D1**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**
Study Treatment[1]															
PF-05212384		X		X	X	X	X	X	X	X	X	X	X	X	X
Cisplatin			X				X			X			X		
Pharmacokinetics															
PK for PF-05212384[2]		X					X			X					
PK for Cisplatin[3]			X				X								

1. **Study Treatment:** Arm B treatment with PF-05212384 will be initiated 7 days prior to Cycle 1 Day 1. On Cycle 1 Day 1 patients will receive cisplatin alone. On Cycle 1 Day 2, patients will receive treatment with PF-05212384 alone. On Day 1 for Cycles 2 and beyond, patients will receive cisplatin followed by PF-05212384.

2. **PK Sampling for PF-05212384:** Blood samples for pharmacokinetics will be taken at 0 hours (pre-dose), 0.5 hours (immediately after the infusion of PF-05212384), 1, 2, 4, 6, 24, 72, 96 and 168 hours post-dose 7 days prior to Cycle 1 Day 1 and on Cycle 2 Day 1. Pre-dose samples will be collected on Day 1 for Cycles 3-6.

3. **PK Sampling for Cisplatin:** Blood samples for pharmacokinetics will be taken at 0 hours (pre-dose), 2 hour (immediately after the infusion of Cisplatin) 2.5, 3, 4, 6, and 24 hours post-dose on Day 1 for Cycles 1 and 2.

SCHEDULE OF STUDY TREATMENT AND PHARMACOKINETIC ASSESSMENTS ARM C (Original Protocol through Amendment 4)

				Cycle 1				Cycle 2			Cycle 3 - 6			Cycle 7 and Beyond		
Protocol Activity	**Screen/ Baseline**	**14 Days prior to C1D1**	**7 Days Prior to C1D1**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**
Study Treatment[1]																
PF-05212384		X			X	X	X	X	X	X	X	X	X	X	X	X
Dacomitinib			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics																
PK for PF-05212384[2]		X						X			X					
PK for Dacomitinib[5]				X				X								

1. **Study Treatment:** Arm C: treatment with PF-05212384 will be initiated 14 days prior to Cycle 1 Day 1. 7 days prior to Cycle 1 Day 1 the patient will initiate dacomitinib which will be taken orally daily. On Cycle 1 Day 1 patients will receive dacomitinib only. On Cycle 1 Day 2, patients will receive treatment with dacomitinib followed by PF-05212384. On Day 1 for Cycles 2 and beyond, patients will receive dacomitinib followed by PF-05212384.

2. **PK Sampling for PF-05212384:** Blood samples for pharmacokinetics will be taken at 0 hours (pre-dose), 0.5 hours (immediately after the infusion of PF-05212384), 1, 2, 4, 6, 24, 72, 96 and 168 hours post-dose 14 days prior to Cycle 1 Day 1 and on Cycle 2 Day 1. Pre-dose samples will be collected on Day 1 for Cycles 3-6.

3. **PK Sampling for Dacomitinib:** Blood samples for pharmacokinetics will be taken at 0 hours (pre-dose), 1, 2, 4, 6, and 24 hours post-dose on Day 1 for Cycles 1 and 2.

Schedule of Activities for Safety and Efficacy Expansion with PF-05212384 plus Cisplatin in Patients with TNBC

		Cycle 1				Cycle 2 and Beyond			End of Treatment[29]	Follow Up[30]
	Screen/ Baseline[1]	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15		
Visit Window				±1 day	±1 day	±2 days	±2 days	±2 days	+7 days	
Informed consent[2]	X									
Tumor history[3]	X									
Medical history[4]	X									
Baseline signs and symptoms[5]	X									
Physical examination[6]	X								X	X
Abbreviated physical examination[6]		X				X				
Weight	X	X				X			X	
Vital signs[7]	X	X				X			X	X
Performance status[8]	X	X							X	X
Laboratory[9] and other Safety Assessments										
Hematology[10]	X	X		X	X	X		X (Cycle 2 only)	X	
Blood chemistry[11]	X	X		X	X	X		X (Cycle 2 only)	X	
Coagulation[12]	X	X				X			X	
Urinalysis[13]	X	X				X			X	
Pregnancy test[14]	X					X			X	
ECG (12-lead)[15]	X	X				X			X	
Tumor Assessments										
CT/MRI scan[16]	X							X (every 6 wks)	X	
Other Clinical Assessments										
Adverse events (AE)[17]	X	→	→	→	→	→	→	→	→	X
Concomitant medications[18]	X	→	→	→	→	→	→	→	→	X
EORTC QLQ-C30, EORTC QLQ BR-23[19]		X		X		X	X			

		Cycle 1				Cycle 2 and Beyond			End of Treatment[29]	Follow Up[30]
	Screen/ Baseline[1]	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15		
Visit Window				±1 day	±1 day	±2 days	±2 days	±2 days	+7 days	
Registration and Study Treatment[20]										
Registration[21]	X									
Pharmacokinetics and Pharmacodynamics[22]										
Mandatory archival FFPE tumor tissue[23]	X									
CCI										
CCI										

Safety laboratory tests (hematology, blood chemistry, urinalysis, coagulation) and tumor assessments may be done up to 72 hours prior to scheduled Day 1 visit on any cycle to facilitate availability of results to Investigator at the time of clinic visit. No time window is allowed for pregnancy test.

Footnotes

1. **Screening/Baseline Assessments:** must be completed within 28 days prior to study treatment start unless otherwise specified as shown in the schedule of events above.
2. **Informed Consent**: must be obtained prior to undergoing any study specific procedures.
3. **Tumor History:** will be collected within 28 days prior to first dose of study treatment. History will include details of treatment history (surgery, systemic treatment and radiotherapy) as well as duration and best response to immediate prior regimen if available. When available, history should include known molecular characteristics of the patient's tumor including mutations, amplifications, etc. (eg, PI3K, PTEN, HER family, AR, etc).

4. **Medical History:** will be collected within 28 days prior to first dose of study treatment. Includes history of disease process other than oncology (active or resolved) and concomitant illnesses. Includes prior treatment including dosing and duration of administration as well as verification of concurrent medication**.**
5. **Baseline Signs & Symptoms:** patients will be asked about any signs and symptoms experienced within the past 14 days of study treatment start. During study treatment, any new or worsened conditions since baseline will be reported on the Adverse Event CRF.
6. **Physical Exam (PE):** performed at Screen/Baseline. EOT and F/U PE will include an assessment for emergent toxicities or changes from prior visits. These procedures may be conducted by the Investigator or his/her designee. Abbreviated physical exams should be performed where a complete physical exam is not required, and on an as needed basis for assessment of adverse events. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.
7. **Vital signs:** will include height (baseline only), weight, blood pressure and heart rate to be recorded in the sitting position after approximately 5 minutes of rest.
8. **Performance status:** per ECOG scale to be assessed within 14 days prior to the first dose of study treatment, and as described in the table above (see Appendix 4).
9. **Laboratory Tests:** will be performed as indicated within 14 days prior to the first dose of study treatment and during treatment (pre-dose) as described in the table above. Additional laboratory tests may be performed when medically indicated.
10. **Hematology:** to include platelet count, hemoglobin, and WBC count with 5-part differential. No need to repeat on day of first dose of study treatment if baseline assessment performed within 7 days.
11. **Blood Chemistry:** to include AST (SGOT), ALT (SGPT), serum creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase, chloride, uric acid, phosphorus, calcium, magnesium, potassium, sodium, BUN or urea, total protein, albumin, glucose (fasting), and insulin. HbA1c at screen/baseline, and then every other cycle or as indicated in the event of suspected hyperglycemia. No need to repeat on day of first dose of study treatment if baseline assessment performed within 72 hours. It is recommended that patients be under fasting conditions (no food or drink within 8 hours) for all blood chemistry panels on Day 1 of each cycle.
12. **Coagulation Tests:** to include partial thromboplastin time (PTT), or abbreviated partial thromboplastin time (aPTT) if PTT not routinely performed, and international normalized ratio (INR). No need to repeat on day of first dose of study treatment if baseline assessment performed within 72 hours.
13. **Urinalysis:** by dipstick is acceptable. Microscopic analyses if dipstick deemed abnormal per Investigator discretion. No need to repeat on day of first dose of study treatment if baseline assessment performed within 72 hours.
14. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once again at least 72 hours prior to Cycle 1 Day 1. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.

15. **ECG:** Triplicate 12-lead ECG (per institutional practice) will be performed. At each time point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval using Fredericia's correction formula. ECGs will be collected as follows:

    - Within 14 days prior to the first dose of study treatment;
    - Day 1 of all Cycles: pre-PF-05212384 infusion and immediately prior to completion of PF-05212384 infusion;
    - End of Treatment Visit.

    The ECG should be collected prior to scheduled PK collections; the timing of the PK collections over rides the timing for ECG collections (ie, if a PK sample is scheduled at 1 hour post dose and an ECG is scheduled 1 hour post dose, then the ECGs should be collected just prior to the hour PK collection, and the PK sample should be collected at the nominal time). If the patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) an ECG should be obtained at time of the event. See Section 7 for additional considerations regarding ECG. If the mean QTc is prolonged (value of ≥500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs may be performed as clinically indicated.

16. **Tumor Assessments:** Tumor assessments will be performed every 6 weeks (±5 days) while the patient is receiving treatment regardless of treatment delays. Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans. A thoracic CT scan should be performed at every tumor assessment independent of lung involvement and in the absence of respiratory symptoms. Brain scans and bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out CNS metastases. Confirmation of response (CR/PR) (at least) four weeks after initial response assessment is required. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. For those patients who discontinue for reasons other than progression of disease, tumor assessments should continue until progression of disease is documented. In patients continuing on study for >12 cycles and have experienced manageable toxicity and stable disease, the interval between imaging assessments may be modified from every 6 weeks (±5 days) to every 9 weeks (±5 days) if the Investigator determines it is in the best interest of the patient, and after discussion and approval by the Sponsor. The modification will decrease the burden on the patients and sites, while still ensuring adequate monitoring for safety and efficacy.

17. **Adverse Event (AE) Assessments:** AEs should be documented and recorded at each visit using NCI CTC AE version 4.03 (Appendix 3). Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy within that time frame. 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 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.

18. **Concomitant Medications:** All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases.

19. **EORTC QLQ-C30 and QLQ-BR23**: Patients must complete all QLQ-C30 and QLQ-BR-23 self-assessment questionnaires in the clinic at the specified time points prior to any other study or medical procedures and prior to any discussion of their progress with the physician or clinic personnel. The questionnaires cannot be taken home. After Cycle 2, all assessments occur on Day 1 of each cycle.

20. **Study Treatment:** Patients will be treated with PF-05212384 once weekly in 3 week cycles. Cisplatin will be given once every 3 weeks. Details on study treatment are provided in the **Schedule of** STUDY TREATMENTS and Pharmacokinetics Assessments.
21. **Registration:** Patient enrollment number assigned by Pfizer Inc. (or designee).
22. **PK Sampling:** Details on sampling are provided in the **Schedule of** STUDY TREATMENTS and Pharmacokinetics Assessments.
23. **Archival tumor biopsy for biomarker analysis:** All patients will be required to provide an archived tumor biopsy formalin fixed paraffin embedded (FFPE) sample. If an archived tumor sample is not available, patients must consent to provide a fresh biopsy FFPE for purpose of this analysis. Patients may not be enrolled into the study without providing either an archived or fresh tumor sample. For the tumor biopsy sample, paraffin blocks are preferred, but freshly cut slides are acceptable. Details for handling of these samples including processing, storage, and shipment will be provided in the Study Manual.

29. **End of treatment visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).
30. **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, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment 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. For those patients who discontinue for reasons other than progression of disease, tumor assessments should continue until progression of disease is documented.

SCHEDULE OF STUDY TREATMENT AND PHARMACOKINETIC ASSESSMENTS – PF-05212384 plus Cisplatin in Patients with TNBC

	Cycle 1				Cycle 2				Cycle 3 - 6			Cycle 7 and Beyond		
Protocol Activity	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**
Study Treatment[1]														
PF-05212384	X		X	X	X		X	X	X	X	X	X	X	X
Cisplatin	X				X				X			X		
Pharmacokinetics														
PK for PF-05212384[2]	**X**	X	X		X	X	X		X					

1. **Study Treatment:** On Cycle 1 Day 1 patients will receive cisplatin followed by PF-05212384 approximately 30 minutes after completion of cisplatin infusion.

2. **PK Sampling for PF-05212384:** Cycle 1 Day 1 and Cycle 2 Day 1: Blood samples for pharmacokinetics will be taken at 0 hours (pre-dose), 0.5 hours (immediately after the infusion of PF-05212384), 1, 2, 4, 6, 24, 72, and 168 (predose Day 8) hours post-dose. Pre-dose samples will be collected on Day 1 for Cycles 3-6.

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APPENDICES

1. INTRODUCTION

1.1. Indication – Original Protocol through Amendment 4

PF-05212384 in combination with other anti-tumor agents (docetaxel, cisplatin, and dacomitinib) is a phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor being developed for use in adult patients with advanced solid tumors.

1.2. Indication – Amendment 5

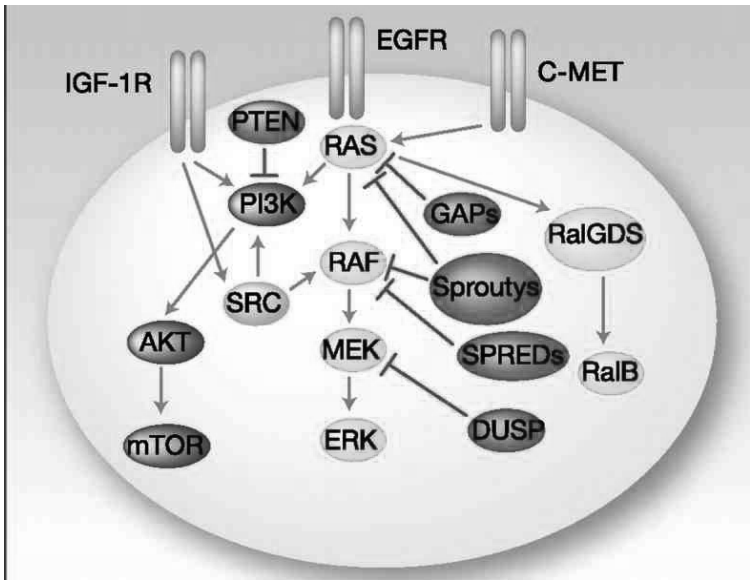
PF-05212384 in combination with cisplatin is being developed for use in adult woman with metastatic or locally-recurrent/advanced triple hormone-receptor negative breast cancer (TNBC) in first- through third-lines of therapy.

1.3. Background

1.3.1. PI3K/mTOR

PI3Ks constitute a lipid kinase family involved in the regulation of diverse cellular processes, including proliferation, survival, cytoskeletal organization, and glucose transport.[1] PI3K enzymes catalyze the formation of the second messenger phosphatidylinositol (3, 4, 5)-trisphosphate (PIP3), which activates many target proteins, most notably phosphoinositide-dependent kinase-1 (PDK1). The downstream targets of these protein kinases, such as mammalian target of rapamycin (mTOR), BCL2-associated agonist of cell death (BAD) and forkhead box O proteins (FOXOs), mediate most of the proliferation, growth and survival signaling from PI3Ks (Figure 3).[2,3] Activation of the PI3K pathway has been implicated in a wide variety of human cancers. Mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA)*, the gene encoding the catalytic subunit of PI3K, are very common in human cancers, having been observed in prostate, and colorectal tumors, among others. Phosphatase and tensin homolog (PTEN) deletion, leading to activation of Akt has been observed in many types of malignancies including prostate cancer, breast cancer, and glioma.[4]

Figure 3. PI3K/mTOR and EGFR Signaling Pathways



Inhibitors of mTOR are in development for the treatment of cancers, most of these agents are analogs of rapamycin, which specifically inhibit the activity of the TORC1 complex.[5,6] Analogs of rapamycin such as CCI-779 (temsirolimus) and RAD-001 (everolimus) have been shown to provide benefit to patients for the treatment of renal cell carcinoma. However, specific inhibition of TORC1 results in a feedback stimulation of Akt and thus inhibition of TORC1 alone may be inferior to inhibition of PI3K and both TORC complexes.[7]

The role of human epidermal growth factor receptor (HER) family members HER-1 (epidermal growth factor receptor (EGFR)), HER-2 (neu/c-erb-2), and HER-3 in many cancer types is well documented. One or more of the members of this receptor family are expressed in over 90% of solid tumors and approximately 60% of those tumors possess abnormalities in this family that potentially contribute to their neoplastic phenotype.[8,9] Over-expression of the HER-2 gene is associated with aggressive neoplastic phenotype and reduced survival in patients with breast cancer. Over-expression of HER-2 has also been correlated with poor prognosis and sensitivity to the anti-HER-2 monoclonal antibody, trastuzumab, in patients with other tumor types including lung, gastric, ovarian, and colorectal carcinomas. EGFR over-expression or aberrant function has been widely noted in lung, renal, prostate, breast, head and neck, colorectal, and other malignancies.[10,11,12] The level of EGFR expression appears to be one factor affecting tumor proliferation, invasiveness, and angiogenesis, and relates adversely to prognosis. In addition, EGFR mutations have been identified which appear to drive tumorigenesis and which determine sensitivity to EGFR targeted agents such as gefitinib.[13,14] HER family members are considered clinically validated targets based on successful development of both biologics and small molecule inhibitors including trastuzumab, lapatanib, erlotinib, cetuximab, and panitumumab.

The PI3K pathway is associated with resistance to a variety of anti-tumor agents. This has been described pre-clinically with cytotoxic chemotherapeutic agents with varying mechanisms of action including taxanes and deoxyribonucleic acid (DNA)-damaging agents.[15,16] In the clinic, activated PI3K in tumors has been correlated with decreased response to therapy and worse clinical outcomes.[17,18,19] In addition to resistance to cytotoxic agents, there is also evidence of PI3K signaling affecting sensitivity of cells to EGF signaling inhibitors. Specifically, the activation of PI3K in tumors has been associated with a worse outcome in patients with HER2-positive gastric cancer treated with anti-HER2 agents.[18] Finally, pre-clinical studies have described the role of the PI3K pathway in EGFR activation in glioblastoma multiforme (GBM) and non-small cell lung cancer (NSCLC) cells and have demonstrated that PI3K inhibitors can reverse resistance to EGFR inhibitors in tumor models.[20]

1.3.2. PF-05212384

PF-05212384 is an ATP-competitive, pan class I PI3K inhibitor, with an IC_{50} of 0.4 nM against PI3Kα and against mTOR with antiproliferative activity in culture and anti-tumor activity in xenograft models. It is intended to be dosed once weekly by intravenous (IV) infusion.

1.3.2.1. Preclinical Data for PF-05212384

PF-05212384 has been shown to cause tumor growth inhibition as well as tumor regressions in a variety of human xenograft tumor models (Table 1). In vivo biomarker studies demonstrated that PF-05212384 suppressed PI3K/mTOR pathway signaling as evidenced by decreased phosphorylation of AKT. These studies were done in MDA361 (human breast) tumor xenografts propagated in nude mice. In this model, pAKT at position T308 was suppressed for 8 hours with PF-05212384 at a dose of 25 mg/kg. Additionally, increased cleaved poly ADP ribose polymerase (PARP), a marker for apoptosis, was observed which correlated with the tumor regression.

Table 1. Tumor Growth Inhibition with Single Agent PF-05212384

Cell Line	Tumor Type	Effects of PF-05212384 Treatment
LST147T	Colon	Growth inhibition
HCT116	Colon	Growth inhibition
BT-474	Breast	Growth inhibition
MDAMB361	Breast	Regression
A549	Non-small cell lung	Growth inhibition
H1975	Non-small cell lung	Growth inhibition
U87MG	Glioma	Stasis
PDX-OV1002	Ovary	Stasis
PDX-HOX516	Ovary	Stasis
MFE296	Endometrial	Stasis
AN3CA	Endometrial	Stasis
MFE280	Endometrial	Regression

1.3.3. PF-05212384 Clinical Experience

PF-05212384 has been evaluated in one completed Phase 1 clinical trial in adult patients with solid cancer, and is being evaluated in two ongoing clinical trials (one Phase 1b study in combination with irinotecan, and one Phase 2 study in endometrial cancer as single agent).

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

The first-in-human (FIH) Phase 1 trial, B2151001 evaluated the safety and pharmacokinetics (PK) of single agent PF-05212384 in patients with advanced solid tumors. PF-05212384 doses ranging from 10 mg to 319 mg weekly were administered to a total of 77 patients using a continuous reassessment method (CRM) to estimate the maximum tolerated dose (MTD). The MTD was decared to be 154 mg, a dose level at which patients received a median number of 7 weekly doses (range 1-24). In general treatment with single agent PF-05212384 was well tolerated over multiple cycles of treatment. Table 2 includes the number of dose limiting toxicities (DLTs) that occurred during the active treatment phase with PF-05212384. Most DLTs occurred at dose levels above the MTD.

Treatment-related adverse events are summarized in Table 3 and Table 4. The most common treatment-related AEs at the MTD (154 mg) were mucosal inflammation and nausea, which were reported in nearly half of the patients (42.9% and 40.5%, respectively), followed by hyperglycemia (26.2%), vomiting (23.8%), and asthenia, decreased appetite, and fatigue (21.4% each). Dysgeusia (19.0%), AST increase, and diarrhea (14.3% each) were also frequent adverse events associated with treatment with PF-05212384. To be noted, although hyperglycemia was reported as an AE in 26.2% of patients at the MTD, the chemistry data showed hyperglycemia in 78.6% of patients treated at the MTD of PF-05212384, although mainly of Grades 1 and 2 (71.4% of all patients treated at the MTD); 3 (7.1%) patients had Grade 3 hyperglycemia.

Three patients discontinued treatment with PF-05212384 due to treatment related adverse events (one patient with increased ALT at the 319 mg dose level, and two patients with mucositis at the 222 mg and 319 mg dose levels, respectively).

Table 2. Phase 1 Study B2151001: Dose Limiting Toxicities by Preferred Term and Dose

Dose Limiting Toxicity by Preferred Term	Dose Level of PF-05212384			
	154 mg (n=42) MTD	222 mg (n=7)	266 mg (n=8)	319 mg (n=4)
Mucosal inflammation Grade 3	1	3	2	1
ALT Grade 3	1	1		
AST Grade 3	1			
Stomatitis Grade 2		1		
Rash Grade 3			2	1
Hyperglycemia Grade 3			1	

Table 3. Phase 1 Study B2151001: Treatment-Related, Treatment Emergent Adverse Events by MedRA Preferred Term in ≥2 Patients; PF 05212384 154 mg Dose Level (MTD) – All CTCAE Grades

PF-05212384 154 mg N=42			
Adverse Event by Preferred Term	**n (%)**	**Adverse Event by Preferred Term**	**n (%)**
Mucosal inflammation	18 (42.9)	Dehydration	3 (7.1)
Nausea	17 (40.5)	Dermatitis acneiform	3 (7.1)
Hyperglycemia	11 (26.2)	Dry skin	3 (7.1)
Vomiting	10 (23.8)	Hypercholesterolemia	3 (7.1)
Asthenia	9 (21.4)	Lymphopenia	3 (7.1)
Decreased appetite	9 (21.4)	Rash	3 (7.1)
Fatigue	9 (21.4)	Abdominal pain upper	2 (4.8)
Dysgeusia	8 (19.0)	Arthralgia	2 (4.8)
Aspartate aminotransferase increased	6 (14.3)	Blood alkaline phosphatase increased	2 (4.8)
Diarrhea	6 (14.3)	Dizziness	2 (4.8)
Alanine aminotransferase increased	5 (11.9)	Hypercalcemia	2 (4.8)
Pyrexia	5 (11.9)	Hyperhidrosis	2 (4.8)
Stomatitis	5 (11.9)	Insomnia	2 (4.8)
Dry mouth	4 (9.5)	Oral herpes	2 (4.8)
Hypertriglyceridemia	4 (9.5)	Proctitis	2 (4.8)
Constipation	3 (7.1)	Pruritus	2 (4.8)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = total number of patients, n = number of patients meeting prespecified criteria

Table 4. Phase 1 Study B2151001: Summary of Treatment-Related, Treatment-Emergent Adverse Events by MedRA Preferred Term; Maximum CTCAE Grades 3, 4, and 5

Adverse Event Preferred Term	**Grade 3**	**Grade 4**	**Grade 5**
	n (%)	**n (%)**	**n (%)**
PF-05212384 (154 mg; N=42)			
Any AEs	10 (23.8)	0	0
Alanine aminotransferase increased	3 (7.1)	0	0
Aspartate aminotransferase increased	2 (4.8)	0	0
Asthenia	1 (2.4)	0	0
Blood alkaline phosphatase increased	1 (2.4)	0	0
Hyperglycemia	1 (2.4)	0	0
Hypersensitivity	1 (2.4)	0	0
Mucosal inflammation	2 (4.8)	0	0
Nausea	1 (2.4)	0	0
Pyrexia	1 (2.4)	0	0
Stomatitis	1 (2.4)	0	0
Urticaria	1 (2.4)	0	0
Vomiting	1 (2.4)	0	0

MedDRA (version 15.1) coding dictionary applied.
Abbreviations: AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, N = Total number of patients, n = number of patients meeting prespecified criteria

Analysis of plasma samples taken after IV administration indicated that PF-05212384 is eliminated with a half-life of 40-65 hours at the highest dose. While the data appeared to indicate that the half life increased with dose, it is considered that this finding was likely to be an artifact of poor assay sensitivity at lower doses. The estimated half life is similar across doses from 89 to 319 mg weekly. Clearance of PF-05212384 is linear with dose, and distribution is relatively high. Plasma concentrations of PF-05212384 exceeded the 50% of maximal inhibition (IC50) of PI3K and mTOR dependent phosphorylation events for approximately 70 hours at doses of 89 and 154 mg, and for ≥120 hours at the 266 mg and 319 mg dose. The target concentration was based on projected human plasma concentration from xenograft models where analysis of xenograft tumor tissue showed a greater than 50% suppression of pAKT and an induction of cleaved PARP, an indicator of cellular commitment to apoptosis.

To date, partial responses (PR) have been observed in 2 patients (NSCLC with liver and lung metastases [n=1] and granular cellular tumor of the ovary with peritoneal and pleural metastases [n=1]) and 19 patients have experienced stable disease (SD), with 6 experiencing SD >6 months.

1.3.3.2. Phase 1 Study of PF-05212384 in Combination with Irinotecan in Patients with Advanced Solid Tumors (B1271002)

A Phase 1b study is ongoing which includes the assessment of escalating doses of PF-05212384 in combination with irinotecan (180 mg/m^2) every 2 weeks of 28-day cycles. To-date, 13 patients have been treated with PF-05212384 at doses of 95 mg/week (n=3), 110 mg/week (n=6), and 130 mg/week (n=4). Two patients out of 4 experienced dose-limiting toxicities, Grade 4 febrile neutropenia (n=1) and Grade 3 fatigue (n=1), while receiving 130 mg/week of P-05212384 plus irinotecan 180 mg/m^2 every 2 weeks. Based on these findings, the MTD for PF-05212384 when combined with irinotecan 180 mg/m^2 every 2 weeks has been determined to be 110 mg/week. The most common treatment-related AEs reported in the 6 patients treated at the MTD include nausea in 3 patients and alopecia, diarrhea, proteinuria, maculopapular rash and vomiting in 2 patients each. All of the events were Grade 1-2. One patient with advanced colorectal cancer (CRC), previously treated with irinotecan, was treated at the PF-05212384 95 mg/week dose cohort and experienced a PR (of 6 cycles in duration). A second patient with CRC previously treated with irinotecan experienced 10% tumor shrinkage and remained on study for 6 months. One patient with pancreatic cancer had tumor shrinkage of 5% and remained on study treatment for 4 months, and one patient with pancreatic cancer had tumor shrinkage of 27% and SD for a duration of 9 cycles.

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

Single agent PF-05212384 is currently being evaluated in patients with advanced endometrial cancer in Phase 2 study B1271004. PF-05212384 is being administered at the MTD dose of 154 mg/week. As of February 5, 2013, 20 patients have been randomized to the PF-05212384 arm of the study. Four patients have achieved clinical benefit as defined by lack of disease progression in first 16 weeks. The preliminary safety profile of PF-05212384 from B1271004 is similar to that from Study B2151001.

Complete information for this compound may be found in the Single Reference Study Document (SRSD), which for this study is the Investigator's Brochure.

1.3.4. Docetaxel

Docetaxel is a semisynthetic taxane whose mechanism of action is to promote tubulin assembly in microtubules and to inhibit their depolymerization which causes cells to arrest in mitosis and eventually undergo apoptosis. Docetaxel is effective in a wide variety of solid tumors and is indicated as a single agent or in combination with other chemotherapeutic agents for the treatment of patients with breast, lung, hormone-refractory prostate, gastric, and head and neck tumors. Docetaxel doses range from 60-100 mg/m^2 depending on the indication and are administered as an infusion every three weeks. Notable toxicities include fluid retention and hypersensitivity reactions.[15] Premedication is required to minimize these adverse event and typically consists of dexamethasone 8 mg twice a day (bid) given for 3 days starting 1 day prior to docetaxel administration. Docetaxel is most commonly associated with myelosuppression and gastrointestinal adverse events.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. Docetaxel is primarily eliminated by fecal excretion.

Complete information for docetaxel may be found in the SRSD, which for this study is the European Union (EU) European Medicines Agency (EMA)-approved Summary of Product Characteristics (SmPC) for Taxotere®.

1.3.5. Cisplatin

Cisplatin reacts in vivo by binding to and causing crosslinking of DNA, ultimately triggering apoptosis. It is used widely as a single agent or in combination with other agents to treat various types of cancer including testicular, bladder, small cell lung, ovarian, and TNBC. Cisplatin doses range from 50-100 mg/m^2 administered IV every 3-4 weeks. In order to mitigate nephrotoxic risks, pre- and post-dose hydration is often used as described in the product label.

Notable toxicities include renal insufficiency, myelosuppresion, nausea and vomiting.

Due to its unique chemical structure, the chlorine atoms of cisplatin are more subject to chemical displacement reactions by nucleophiles, such as water or sulfhydryl groups, than to enzyme-catalyzed metabolism. Cisplatin is not metabolized hepatically. Cisplatin is excreted through the urine.

Complete information for cisplatin may be found in the SRSD, which for this study is the United Kingdom (UK) approved Summary of Product Characteristics (SmPC) from Hospira UK Ltd.

1.3.5.1. PF-05212384 Plus Cisplatin in Patients with TNBC

The rationale for combining cisplatin with PF-05212384 in patients with metastatic or locally-recurrent/advanced triple hormone-receptor negative breast cancer (TNBC) is two-fold: First, there is amplified genomic instability of TNBC tumor cells, leading to an increased vulnerability of TNBC to DNA-damaging agents, such as cisplatin. TNBC tumor cells harbor activating mutations in the PIK3CA gene, making these cells excellent targets for inhibition of the PI3K pathway using pathway inhibitors, such as PF-05212384.[46]

In addition, some fraction of TNBC tumor cells (~20%) harbor mutations in the DNA repair genes breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2), suggesting a functional deficit in the process of homologous recombination repair (HRR) of DNA. The inability to repair DNA efficiently makes these cells particularly susceptible to the DNA cross-link strand breaks caused by platinating agents, like cisplatin.[40,46]

The use of cisplatin in combination regimens in patients with TNBC has shown improved rates of tumor response in both the neoadjuvant and metastatic setting.[40,50] As such, recent National Comprehensive Cancer Network® (NCCN) guidelines for treatment of metastatic TNBC have included platinum salts, such as cisplatin.[51]

The above information provides a sound rationale for combining PF-05212384 with cisplatin in the treatment of patients with metastatic TNBC.

1.3.6. Dacomitinib (PF-00299804)

The investigational agent dacomitinib is an orally available, selective ATP-competitive irreversible small-molecule inhibitor of Human Epidermal Growth Factor Receptor (HER, erbB) family receptor tyrosine kinases (RTKs). This family of RTKs includes the epidermal growth factor receptor (EGFR, HER-1), HER-2 receptor (erbB2), and HER-4 (erbB4) receptor and their oncogenic variants (ie, EGFR exon 19 deletion, EGFR L858R point mutation, and EGFR T790M mutation). Dacomitinib inhibits the tyrosine kinase activity of the HER family through binding at the adenose triphosphate (ATP) binding site, which results in covalent modification of a cystine in the ATP binding pocket. HER-1 and -2 receptor mutations and amplification have been investigated as possible favorable predictors of clinical efficacy and, in particular, it has been shown that patients with certain mutations of EGFR (exon 19 deletions and exon 21 L858R mutations) have significant benefit from EGFR Tyrosine Kinase Inhibitor (TKI). Dacomitinib is being developed for patients with previously treated, locally advanced or metastatic non-small cell lung cancer (NSCLC).

Dacomitinib given orally without food in the FIH dose escalation study, A7471001, was absorbed with a median time to the maximum observed concentration (T_{max}) ranging from 4 to 24 hours. There was no evidence of a clinically relevant effect of antacid administration on C_{max} and AUC_{inf} (defined as area under the plasma concentration-time profile from time zero to infinity time) of dacomitinib. In general, the mean C_{max} and AUC of PF-00299894 increased with dose at the dose range evaluated. After continuous once daily oral dose (QD) for 14-days, the mean AUC accumulation of dacomitinib ranged from 4.39 to 6.18-fold,

suggesting a long $t_{½}$. Inter-patient variability in PK exposure parameters varied from 14-65%. There was no evidence of increasing trough concentrations with time when examining available predose concentrations on Cycle 2 Day 1, 8, and 14 in a limited number of patients (n=2-4) at 45 mg. To date, the terminal $t_{½}$ has been characterized in patients at 45 mg, and ranged from 75 to 110 hour with a mean of approximately 85 hours.

Dacomitinib is metabolized in part by cytochrome P450 2D6 (CYP2D6) and an active metabolite, PF-05199265, is formed. Dacomitinib also inhibits the CYP2D6 metabolic pathway. Collectively results from clinical studies suggest that dacomitinib may increase exposure of other drugs primarily metabolized by CYP2D6 and therefore administration of drugs which are highly dependent on CYP2D6 metabolism may require dose adjustment, or substitution with an alternative medication. Dacomitinib is mainly eliminated by fecal excretion.

Dacomitinib is currently in Phase 3 development in advanced NSCLC. As of 16 May 2012, 1503 patients with advanced cancer have been enrolled and treated in 13 clinical trials evaluating the safety, efficacy and pharmacokinetics of dacomitinib. Of these 1503 patients, 579 patients were administered dacomitinib as single agent, 466 patients received either dacomitinib or placebo as double-blinded therapy, 293 patients received either dacomitinib or erlotinib as double-blinded therapy, 71 patients received dacomitinib in combination with CP-751,871 (figitumumab). Patients have also been treated with dacomitinib in combination with crizotinib.

Complete information for dacomitinib may be found in the SRSD, which for this study is the Investigator's Brochure (IB).

Overall, the adverse events associated with dacomitinib single agent have been considered manageable, reversible, and consistent with class-effects associated with EGFR TKIs. Table 5 provides a summary of the most common treatment-related AEs reported for single agent dacomitinib (all patients, all doses, all grades).

Table 5. Summary of Treatment-Related Adverse Events in ≥10% of Patients Treated with Single-Agent Dacomitinib

Adverse Drug Reaction	**All Grades N=526 N (%)**
Diarrhea	435 (82.7)
Dermatitis acneiform	309 (58.7)
Fatigue	224 (42.6)
Dry skin	186 (35.4)
Stomatitis	171 (32.5)
Paronychia	136 (26)
Decreased appetite	166 (31.6)
Nausea	155 (29.5)
Paronychia	138 (26.2)
Pruritus	115 (21.9)
Vomiting	110 (20.9)
Cough	98 (18.6)
Dyspnoea	92 (17.5)
Mucosal inflammation	91 (17.3)
Rash	91 (17.3)
Palmar-plantar erythrodysaesthesia syndrome	78 (14.8)
Weight decreased	70 (13.3
Constipation	68 (12.9)
Skin fissures	66 (12.5)
Epistaxis	62 (11.8)
Exfoliative rash	62 (11.8)
Back pain	58 (11)
Abdominal Pain	55 (10.5)

Table 6 provides a summary of the most common treatment-related AEs reported following treatment with dacomitinib at 45 mg QD in patients with advanced NSCLC.

Table 6. Summary of Treatment Related Adverse Events in ≥10% of Patients with NSCLC Treated with Dacomitinib at a Dose of 45 mg QD

Adverse Drug Reaction	All Grades N=262 N (%)	Grades ≥3 N=262 N(%)
Diarrhea	212 (80.9)	29 (11.1)
Dermatitis acneiform	170 (64.9)	19 (7.3)
Fatigue	97 (37)	14 (5.3)
Decreased appetite	81 (30.9)	3 (1.1)
Stomatitis	81 (30.9)	3 (1.1)
Dry skin	80 (30.5)	1 (0.4)
Paronychia	75(28.6)	10 (3.8)
Nausea	69 (26.3)	3 (1.1)
Pruritus	50 (19.1)	4 (1.5)
Mucosal inflammation	46 (17.6)	2 (0.8)
Exfoliative rash	35 (13.4)	4 (1.5)
Cough	44 (16.8)	7 (2.7)
Vomiting	43 (16.4)	7 (2.7)
Weight decreased	36 (13.7)	0 (0)
Exfoliative rash	35 (13.4)	4 (1.5
Constipation	32 (12.2)	1 (0.4)
Palmar-plantar erythrodysaesthesia syndrome	30 (11.5)	1 (0.4)

1.3.7. Study Rationale

Signaling through the PI3K pathway is associated with resistance to a variety of anti-tumor agents. This has been described pre-clinically with cytotoxic chemotherapeutic agents with varying mechanisms of action including taxanes, and DNA-damaging agents.[22,23] In the clinic, activated PI3K pathway in tumors has been correlated with decreased response to therapy and worse clinical outcomes.[18,19]

In addition to resistance to cytotoxic agents, there is also evidence of PI3K signaling affecting sensitivity of cells to EGF receptor family signaling inhibitors. Specifically, the activation of PI3K in tumors has been associated with a worse outcome in patients with HER2-positive gastric cancer treated with anti-HER2 agents.[24] In addition, pre-clinical studies have described the role of the PI3K pathway in EGFR activation in glioblastoma multiforme (GBM) and NSCLC cells and have demonstrated that PI3K inhibitors can reverse resistance to EGFR inhibitors in tumor models.[20]

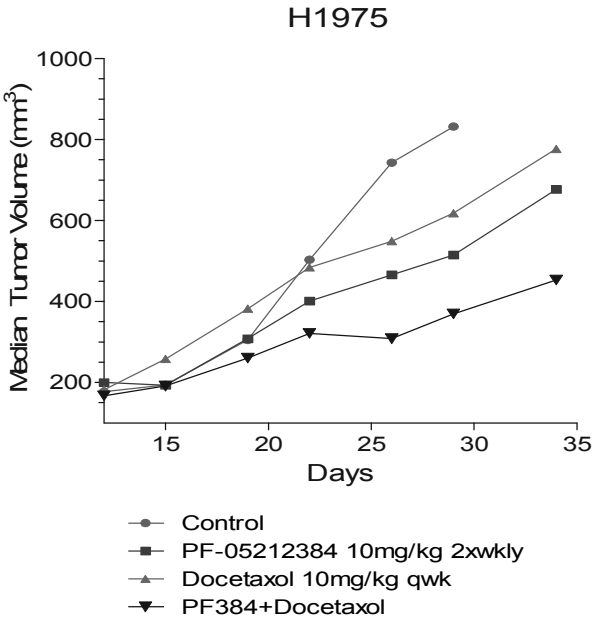
Collectively, these findings suggest that PI3K/mTOR inhibitors may increase the efficacy of both chemotherapeutic agents which are considered standard of care (SOC) for the treatment of several solid tumors and dacomitinib which has shown clinical activity in several tumor types.

1.3.7.1. Rationale for Combinations

1.3.7.1.1. Docetaxel

Docetaxel is a microtubule inhibitor which is active in a number of human solid tumors. In pre-clinical *in vitro* studies, the combination of docetaxel and a PI3K inhibitor resulted in additive and even synergistic activity in a variety of human cancer cell lines. *In vivo* experiments revealed enhanced anti-tumor efficacy with the combination.[16] Non-clinical experiments in human NSCLC H1975 and H1650 xenograft models have demonstrated that the combination of PF-05212384 and docetaxel is more effective than either drug alone (Figure 4). Finally, patients with tumors with activated PI3K/Akt signaling have been shown to be less responsive to a variety of chemotherapeutic agents including docetaxel and paclitaxel.[17,18] The pre-clinical findings together with the clinical observations, suggest that the addition of PF-05212384 to docetaxel may lead to enhanced antitumor effects in patients.

Figure 4. Tumor Growth Inhibition of PF-05212384 in Combination with Docetaxel Versus either compound alone in H1975 Lung Xenograft Model



1.3.7.1.2. Cisplatin

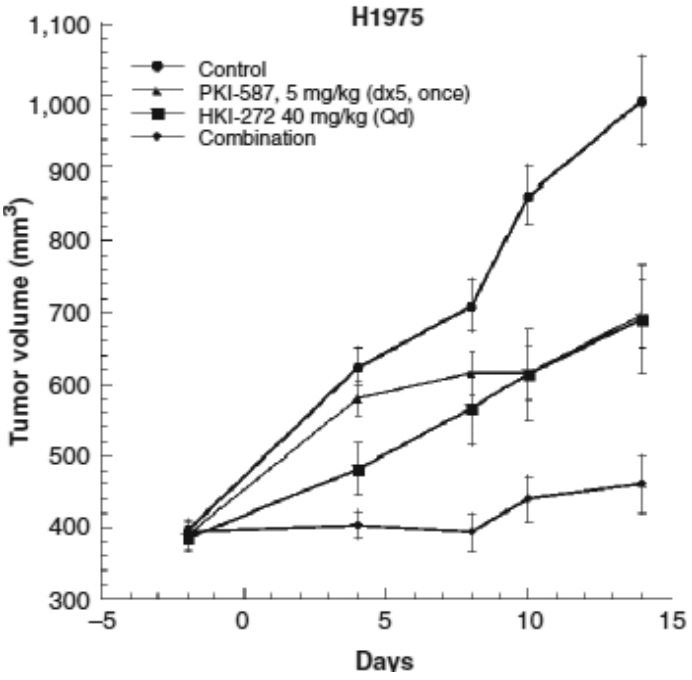
Cisplatin is an alkylating agent which cross-links DNA. Preclinically, the combination of PI3K inhibitor and cisplatin resulted in synergistic anti-tumor activity in human ovarian cancer cell models.[15] Furthermore, the combination of PF-05212384 and cisplatin demonstrated increased anti-tumor efficacy in a breast PDX xenograft model (PJC10). Since single-agent cisplatin is active in patients with triple-negative breast cancer (TNBC) the combination of PF-05212384 and cisplatin may be an extremely effective regimen in an area of great medical need.[24] Cisplatin is also used in combination with gemcitabine in a number of tumor types such as urothelial transitional cell cancers (TCC), NSCLC, and biliary tract tumors and in combination with other chemotherapeutic agents in ovarian cancer (OC).

Thus, based on the preclinical evidence of additive or synergistic activity, once the clinical safety and tolerability of the combination of PF-05212384 and cisplatin has been established, it may be possible to consider replacing gemcitabine with PF-05212384 in these regimens.

1.3.7.1.3. Dacomitinib

EGFR and HER2 are important mediators of tumorogenesis in a number of tumors and PI3K is a critical EGFR-dependent effector of downstream signaling. Activation of the PI3K pathway has been shown to be associated with resistance to HER2 inhibition. This is supported by the observation that in patients with HER2+ gastric cancer, activated PI3K signaling predicts for a worse clinical outcome.[25] Further evidence of cross-talk between the EGFR and PI3K pathways exists in glioblastoma and NSCLC models.[20,26] In a preclinical NSCLC model, the addition of a PI3K inhibitor to gefitinib was shown to overcome resistance to gefitinib.[20] Finally, in the H1975 lung xenograft model, tumor growth inhibition was observed for the combination of PF-05212384 with neratinib, a EGFR and HER2 inhibitor suggesting that the combination with the pan-HER inhibitor dacomitinib might also be beneficial (Figure 5).[27]

Figure 5. Tumor Growth Inhibition of PF-05212384 in Combination with HKI-272 (irreversible Her2 inhibitor) in H1975 Lung Xenograft Model



These data support the evaluation of the combination of PF-05212384 and dacomitinib.

1.3.7.2. Rationale for PF-05212384 Doses

In Phase 1 study B2151001, single agent PF-05212384 at doses ranging from 10 mg to 319 mg weekly (QW) were evaluated in 77 patients with advanced solid tumors. The MTD was identified as 154 mg QW. In study B1271002, PF-05212384 doses of 95, 110, and 130 mg/week were evaluated in combination with irinotecan 180 mg/m^2 every 2 weeks; the MTD of PF-05212384 was 110 mg/week when dosed in combination with irinotecan.

In the current trial, the PF-05212384 starting dose in all 3 treatment arms will be 90 mg/week which is 58% of the MTD for single agent PF-05212384 and slightly lower than the lowest dose evaluated in Phase 2 study B1271002 investigating PF-05212384 in combination with irinotecan. In the Phase 1 FIH trial (B2151001), PF-05212384 dose of 89 mg/week (n=4) was found to result in drug concentrations above the target concentration for approximately 70 hours.

1.3.7.3. Rationale for Docetaxel, Cisplatin and Dacomitinib Starting Doses

In Arm A, the starting dose of docetaxel will be 75 mg/m^2 every 3 weeks. This is the dose recommended in combination with doxorubicin and cyclophosphamide for breast cancer, in combination with prednisone in hormone refractory prostate cancer, and as single agent in NSCLC.[28]

In Arm B, the starting dose of cisplatin will be 75 mg/m^2 every 3 weeks which is the dose often used when it is administered as an every 3 week regimen in combination with docetaxel, gemcitabine, or pemetrexed.[29,30,31]

In Arm C, the starting dose of dacomitinib will be 30 mg which is 67% of the MTD for single agent dacomitinib when administered orally once daily on a continuous dosing schedule. This starting dose was selected given the potential for overlapping toxicity with PF-05212384, such as mucositis and rash. In the dacomitinib FIH trial in patients with advanced tumors, among 111 patients treated in dose-escalation, 13 were treated at the 30 mg/day dose level. One DLT (mucositis) was observed in this group. The safety profile in the specific dose levels was not reported.[32] As described in the IB, the 30 mg dose has only been evaluated in a small number patients in subsequent trials however the 30 mg dose is generally better tolerated than the 45 mg dose.

During the course of the trial, dose reductions for each combination will be permitted in individual patients who cannot tolerate the starting dose (Section 5.2.5).

1.4. Overall Risk Benefit Assessment

Pfizer considers that the results of the nonclinical toxicity and safety pharmacology studies, together with the clinical experience obtained to date with PF-05212384 support the continued development of PF-05212384 in combination with other anti-tumor agents. The tumor types in which these combinations will likely be used, all represent areas of high medical need.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives – Original Protocol through Amendment 4

Primary Objective

- To assess the safety and tolerability and to estimate the MTD of the following combinations in patients with advanced solid tumors:
    - Arm A: PF-05212384 and docetaxel.
    - Arm B: PF-05212384 and cisplatin.
    - Arm C: PF-05212384 and dacomitinib.

Secondary Objectives

- To evaluate the overall safety profile.
- To assess the effects of PF-05212384 on the pharmacokinetics of docetaxel, cisplatin and dacomitinib and *vice versa* in Arms A, B, and C respectively.
- To evaluate possible biomarkers of efficacy (eg, *KRAS* mutation) and pharmacodynamic (PD) effects in paired tumor biopsies (eg, pAkt levels) and serum (eg, insulin levels).
- To characterize the effects of the combinations on the potential to prolong the QTc interval.
- To document anti-tumor activity.

2.2. Endpoints – Original Protocol through Amendment 4

Primary Endpoint

- Dose Limiting Toxicity (DLT).

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.
- Vital sign abnormalities.
- Single and multiple dose PK parameters of PF-05212384, and other anti-tumor agents (docetaxel, cisplatin or dacomitinib) alone and together, respectively.

- Gene sequence data (eg, *PIK3CA*, *KRAS)* and levels of PI3K pathway protein biomarkers (eg, pAkt, PTEN, circulating insulin).

- QTc interval.

- Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

2.3. Objectives - Safety and Efficacy Expansion in Patients with TNBC

Primary Objective

- To evaluate the anti-tumor activity of PF-05212384 plus cisplatin in patients with TNBC.

Secondary Objectives

- To continue to evaluate the overall safety profile of the combination of PF-05212384 plus cisplatin.

- To characterize single and multiple dose pharmacokinetics following IV administration of PF-05212384.

- To characterize the effects of the combinations on the potential to prolong the QTc interval.

- To evaluate additional anti-tumor activity.

- To assess patient reported outcomes (PRO) of global quality of life (QOL) and disease/treatment-related symptoms of advanced breast cancer.

CCI

[redacted]

2.4. Endpoints - Safety and Efficacy Expansion in Patients with TNBC

Primary Endpoint

- Objective response (OR) as assessed by the Investigator using RECIST version 1.1.

Secondary Endpoints

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

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.03) and timing.
- Single and multiple dose PK parameters of PF-05212384.
- QTc interval.
- Clinical Benefit Response (CBR), Duration of Response (DR) and PFS (as assessed using RECIST version 1.1).
- Time to deterioration in global QOL.
- Change from baseline in global QOL and disease/treatment-related symptoms.

CCI [redacted]

[redacted]

3. STUDY DESIGN

This is a Phase 1b, three-arm, open-label, multi-center, multiple dose, dose escalation, safety, tolerability, pharmacokinetic and pharmacodynamic study of PF-05212384 in combination with anti-tumor agents in sequential cohorts of adult patients with select advanced solid tumors. Successive cohorts of patients will receive selected doses of PF-05212384 in combination with selected doses of chemotherapeutic agents or dacomitinib in 3 independent arms on an outpatient basis. Based on the tolerability of PF-05212384 at higher doses in other (monotherapy) studies, the study will test increasing doses of PF-05212384 in combination with docetaxel, cisplatin, and/or dacomitinib in order to select the best dose to administer in the MTD expansion portion of the study.

A modified toxicity probability interval (mTPI) method with adjustment based on observed DLT rate will be used to guide the dose assignment in Arms A and B.[33,34] The actual dose selected for the next cohort will take into account the recommended dose by using the adjusted mTPI method as well as safety data other than DLTs. In Arm C in order to evaluate concurrent doses of dacomitinib in combination with two concurrent doses of PF-05212384, a zone-based design will be utilized, which is a modified 3+3 design that potentially allows opening of more than one dose level at the same time.[35] In all arms, dose escalation will proceed until an MTD (or two MTDs) is declared, or the Maximum Allowable Dose is reached.

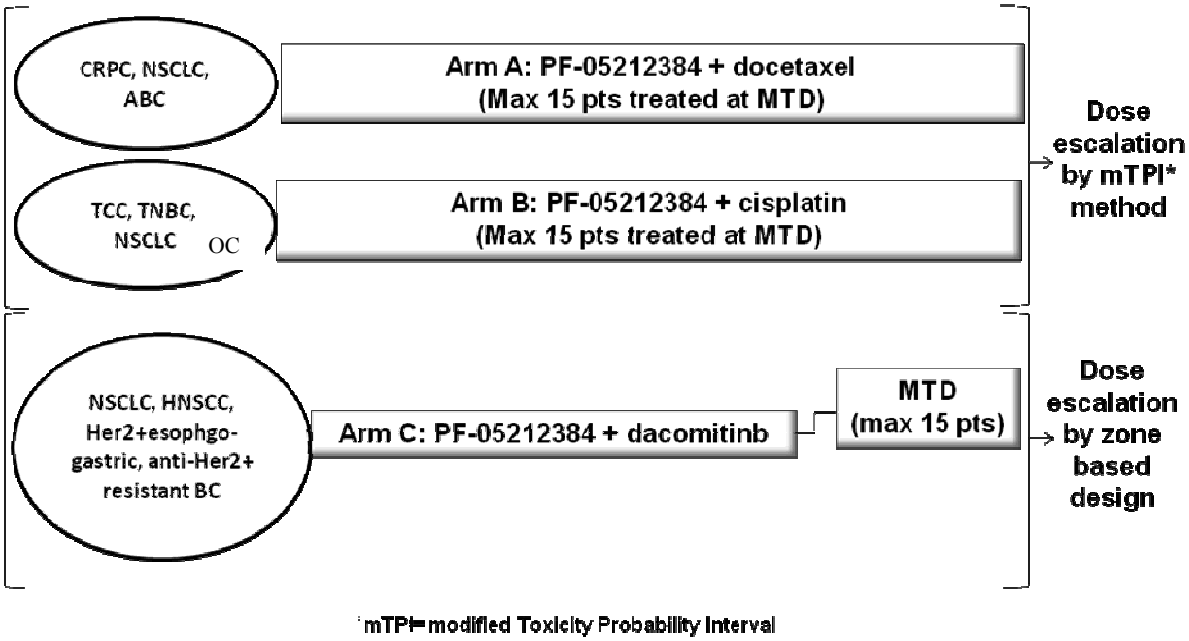
On April 1, 2015, Pfizer Inc. decided to stop enrolment in Arms A and C of the B2151002 clinical trial. Patients previously identified for enrolment in Arm A and C were permitted to enter the study after notification of the decision. Due to closure, the MTD of those combinations will not be established. All references to objectives, endpoints, study design, assessments, etc. and analysis of data in Arm A and C will be limited to the number of

patients treated up to the enrolment discontinuation date for each Arm (June 10, 2015 for Arm A and 06 July 2015 for Arm C). The decision is based on the company's change in prioritization for the portfolio and is not due to any safety/efficacy concerns or regulatory interactions.

For Arm B, the study was originally designed as a dose escalation study with no expansion cohorts. However, Protocol Amendment 5 includes the rationale and description for the safety and efficacy expansion with PF-05212384 plus cisplatin in patients with metastatic or locally-recurrent/advanced triple hormone-receptor negative breast cancer (TNBC). A total of 21 patients were enrolled in Arm A, 33 in Arm B and 33 patients in Arm C in the dose escalation. Approximately 124 patients are expected overall including the safety and efficacy expansion. Pharmacodynamic studies will be performed in paired tumor biopsies, when clinically feasible, to evaluate PI3K and mTOR pathway inhibition at the PF-05212384 doses used in the MTD. Paired biopsies that are obtained during dose escalation and expansion will also be evaluated for modulation of PI3K signaling.

Each of the treatment arms are restricted to patients with tumor types for which the combination partner is either considered standard-of-care, or in the case of dacomitinib, are indications which have been shown to be sensitive.

Figure 6. Original Overall Study Design



CRPC: Castrate resistant prostate cancer; NSCLC: Non-small cell lung cancer; ABC: Advanced breast cancer; TCC: Transitional cell cancer; TNBC: Triple negative breast cancer; OC: ovarian cancer; HNSCC: Head and neck squamous cell cancer; BC: Breast cancer.

To understand the single-dose safety and single dose PK of the study drug, a lead in period will be included. A single lead-in dose of PF-05212384 will be given either 7 days prior to Cycle 1 Day 1 (Arms A and B) or 14 days prior to Cycle 1 Day 1 (Arm C). The lead in period duration, subsequent doses, regimens and PK time-points may be modified based on the PK profile observed during the lead in period. Patients will then receive study treatment on an outpatient basis in 21 day cycles.

Treatment with study drug will continue until progression of disease, uncontrollable toxicity, a decision by the patient or Investigator to discontinue treatment, or the study is terminated. Patients experiencing toxicity or a DLT may be managed with dose modification or discontinuation. If a patient discontinues PF-05212384 or the combination partner (cisplatin, docetaxel, or dacomitinib) due to toxicity which is specific to either agent, continuation of patient treatment within the study with single agent PF-05212384, cisplatin, docetaxel, or dacomitinib will be discussed with the Sponsor on a case-by-case basis.

The proposed doses, schedule(s) and PK timepoints may be reconsidered and amended during the study based on the emerging safety and pharmacokinetic data.

3.1. Dose Levels to Be Tested

The possible dose levels for Arms A, B, and C are shown in Table 7. For Arms A and B, dose levels differ only in the dose of PF-05212384. For Arm C, dose levels differ for PF-05212384 and dacomitinib.

During the dose-escalation portion, patients who have not experienced DLT at the lower doses will be treated at the next cohort which has been cleared for safety (the dose level has not been determined to exceed the MTD). The decision regarding the implementation of intra-patient dose escalation in patients treated at the MTD expansion will be considered once the MTD has been identified.

Table 7. Dose Levels for Arms A, B and C

Arm A		
Dose Level	**PF-05212384 mg/wk IV**	**Docetaxel mg/m^2 IV q 3 wks**
A(-1)	75	75
A1#	90	75
A2	110	75
A3	130	75
A4	150	75
A5	180	75
A6*	215	75
A7*	260	75
A8*	310	75

Starting dose level.

* April 1, 2015, Pfizer Inc. decided to stop enrollment in Arm A.

Arm B		
Dose Level	**PF-05212384 mg/wk IV**	**Cisplatin mg/mg^2 IV q 3wks**
B(-1)	75	75
B1#	90	75
B2	110	75
B3	130	75
B4	150	75
B5	180	75
B6	215	75
B7	260	75
B8	310	75

Starting dose level.

Arm C		
Dose Level	**PF-05212384 mg/wk IV**	**Dacomitnib PO mg qd**
C1#	90	30
C1h	90	45
C2	110	30
C2h†	110	45
C3	130	30
C3h†	130	45
C4	150	30
C5*	180	30
C6*	215	30
C7*	260	30
C8*	310	30

Starting dose level.

† Dose level previously determined to exceed the MTD.

* April 1, 2015, Pfizer Inc. decided to stop enrollment in Arm C.

3.1.1. Criteria for Dose Assignment

3.1.1.1. Criteria for Dose Assignments for Arms A and B

In Arms A and B, a modified toxicity probability interval (mTPI) method with adjustment based on observed DLT rate will be used to guide the dose assignment. The statistical description of the method is provided in Section 9. The dose assignment recommendations of the method are provided in Figure 7. Patients are enrolled in cohorts of 3 patients. In the first cohort, the starting dose level will be assigned as noted in Table 7. For any subsequent cohort of patients, the recommended dose assignment action will be based on the total number of patients with DLTs in the current and prior cohorts treated at the same dose level. For example, if a cohort of 3 patients are treated at dose level A1 for the first time and one of them experiences a DLT, then the recommended action for the next cohort of patients will be to stay at the current dose level (S); if this recommendation is accepted, then the selected dose level for the next cohort of patients will be A1; if a cohort of 3 additional patients are treated at dose level A1 and there are no more DLTs observed, then the cumulative number of patients treated at A1 is 6, and the cumulative number of patients with DLTs at A1 is 1, thus the recommendation would be to escalate the dose for the subsequent cohort (E).

Figure 7. Recommended Action Based on Cumulative DLT Data at the Current Dose Level (Arms A and B)

Cumulative number of patients with DLTs at the current dose level	Cumulative number of patients treated at the current dose level													
	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E	E	E	E	E	E	E
2	D	D	D	D	D	S	S	S	S	E	E	E	E	E
3		DU	DU	DU	D	D	D	D	S	S	S	S	S	S
4			DU	DU	DU	DU	DU	D	D	D	D	S	S	S
5				DU	DU	DU	DU	DU	DU	D	D	D	D	D
6					DU	DU	DU	DU	DU	DU	DU	DU	D	D
7						DU	DU	DU	DU	DU	DU	DU	DU	DU
8							DU	DU	DU	DU	DU	DU	DU	DU
9								DU	DU	DU	DU	DU	DU	DU
10									DU	DU	DU	DU	DU	DU
11										DU	DU	DU	DU	DU
12											DU	DU	DU	DU
13												DU	DU	DU
14													DU	DU
15														DU

E = Escalate to the next higher dose level

S = Stay at the current dose level

D = De-escalate to the next lower dose level

DU = The current dose level is unacceptably toxic and should be eliminated from further testing

Initially up to 3 patients will be treated in a cohort; occasionally, due to logistical reasons, more than 3 but no more than 6 patients may be enrolled in a cohort. Patients not evaluable for assessment of DLT, as described in Section 9.1 may be replaced. The actual dose level selected for the next cohort of patients will take into account the recommended dose level from Figure 7 and all available safety data other than DLTs. Dose-finding for an arm may be stopped when one of the following criteria is met:

- The lowest dose level appears too toxic after at least 3 patients are dosed at that dose level.

- The maximum sample size in dose finding of 40 evaluable patients per arm has been reached.

- A minimum of 10 evaluable patients have been treated at the estimated MTD.

DLTs occurring in the first cycle will be used for determining the starting dose in the subsequent cohort.

All significant AEs and SAEs will be reviewed by the Sponsor and the Investigators to determine if the dose allocation schedule requires modification.

3.1.1.2. Criteria for Dose Assignment for Arm C

A zone-based design will be employed for Arm C.[35] It is a modified 3+3 design that potentially allows opening of more than one dose level at the same time. The starting dose level is C1. Dose escalation will proceed according to the sequence in Table 8 until an MTD (or two MTDs) is declared, or the Maximum Allowable Dose is reached.

Table 8. Dose Escalation Sequence (Arm C)

Arm C			
		Dacomitinib PO mg qd	
		30	45
PF-05212384 mg/wk IV	90	C1#	C1h
	110	C2	C2h
	130	C3	C3h
	150	C4	
	180	C5*	
	215	C6*	
	260	C7*	
	310	C8*	

Starting dose level.
* April 1, 2015, Pfizer Inc decided to stop enrollment in Arm C.

As in a classical 3+3 design, dose escalation is indicated if there is no DLT in 3 patients or ≤1 DLT in 6 patients at the current dose level. If DLT data at dose level C1 indicates dose escalation, then two separate dose escalations from C1 to C2 and from C1 to C1h may occur simultaneously (as shown in Table 8). To open dose level C2h, the DLT data from the preceding two lower dose levels C2 and C1h must both indicate dose escalation, ie, no DLT observed in 3 patients or ≤1 DLT in 6 patients for each of them.

At each dose level, up to 3 patients will be enrolled initially and evaluated for DLT. Subsequent dose levels may not be opened until all patients entered at the current dose level have been treated and observed for at least one complete cycle and the number of DLTs among those patients in their first cycle has been determined. Patients not evaluable for assessment of DLT, as described in Section 9.1, may be replaced. Dose escalation will continue until the Maximum Allowable Dose level is reached or until DLTs are observed in at least 2 of the 3-6 patients treated at a dose level, leading to the conclusion that an MTD has been exceeded. The planned cohort size is 3-6 patients per dose cohort however, based upon observed toxicity or unexpected clinical findings, individual dose cohorts may be expanded beyond 6 patients after discussion and review by the Sponsor's medical monitor and the Investigators. When a dose level exceeding an MTD has been identified, the next lower dose level is declared the MTD if 6 patients have already been treated at that dose level. Otherwise 3 additional patients are treated at the next lower dose level, and if zero or 1 patient experiences DLTs that dose level is declared the MTD.

For Arm C, it is possible that more than one MTD is identified. In such case, the Sponsor in agreement with the Investigators will decide, based on all available data, the most rational dose level to enroll additional patients.

3.2. DLT Definition (All Arms)

Severity of adverse events will be graded according to CTCAE version 4.03. For the purpose of dose escalation, any of the following adverse events occurring in the first cycle of treatment (starting from the lead-in dose through Cycle 2 Day 1) which are possibly attributable to the combination will be classified as DLTs:

- Hematologic:
    - Grade 4 neutropenia lasting >7 days.
    - Febrile neutropenia (defined as neutropenia ≥ Grade 3 and a single body temperature >38.3°C or a sustained temperature of ≥38°C for more than one hour).
    - Grade ≥3 neutropenia with infection.
    - Grade 3 thrombocytopenia with bleeding.
    - Grade 4 thrombocytopenia.

- Non-hematologic:
  - Grade ≥2 pneumonitis.
  - Grade ≥3 toxicities, except pneumonitis, and excluding those that have not been maximally treated (eg, nausea, vomiting, diarrhea, hyperglycemia, rash, mucositis).
  - Persistent, intolerable toxicities which result in the failure to deliver at least 3 of the 4 doses of PF-05212384 during the 1st cycle (including the lead-in dose).
  - Arm A and B: Persistent, intolerable toxicities which result in the failure to deliver at least 3 of the 4 doses of PF-05212384 during the 1st cycle (including the lead-in dose).
  - Arm C: Persistent, intolerable toxicities which result in the failure to deliver at least 3 of the 4 doses of PF-05212384 and 75% of dacomitinib during the 1st cycle (including the lead-in dose(s)).
  - Persistent, intolerable toxicities which result in the delay of the start of the second cycle by more than 2 weeks relative to the scheduled start.
  - In an asymptomatic patient, Grade 3 mean QTc prolongation (QTc ≥501 msec) will first require repeat testing, re-evaluation by a qualified person, and correction of reversible causes such as electrolyte abnormalities or hypoxia for confirmation. If, after correction of any reversible causes, the Grade 3 QTc prolongation persists, then the event should be considered a DLT.

3.3. MTD Definition

For Arms A and B, the MTD will be estimated based on isotonic regression (refer to Section 9 for details) at the end of the study. Up to a maximum of 15 patients will be treated at the MTD during dose finding to define the tolerability and to evaluate clinical activity.

For Arm C, upon identification of the MTD, additional patients up to a maximum of 15 will be treated at the MTD to better define the tolerability and to evaluate clinical activity.

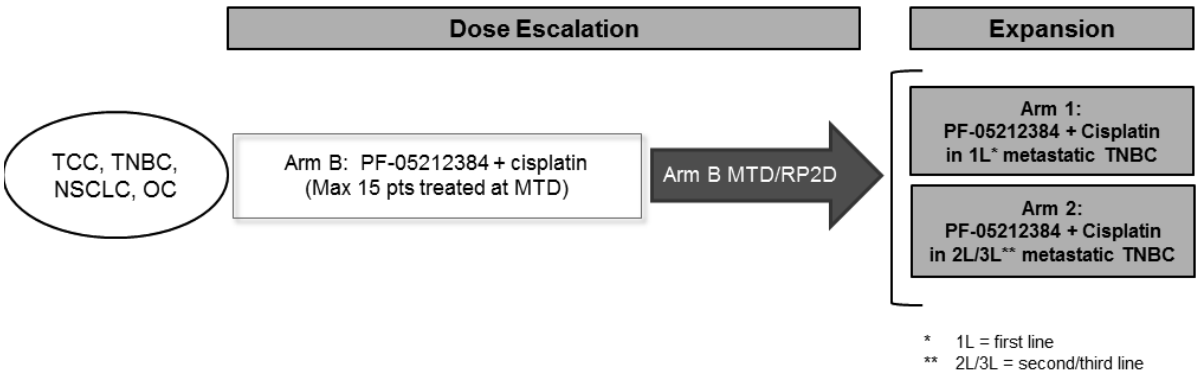
3.4. Safety and Efficacy Expansion in Patients with TNBC

Based on the rationale provided in Section 1.3.5.1, an expansion cohort will open with implementation of Protocol Amendment 5 to assess the clinical activity and continued overall safety profile of PF-05212384 in combination with cisplatin in patients with TNBC. The design is shown in the Figure 8 below.

Treatment in the expansion portion of the study will continue until progression of disease, uncontrollable toxicity, a decision by the patient or Investigator to discontinue treatment, or the study is terminated. Patients experiencing toxicity may be managed with dose modification or discontinuation. If a patient discontinues PF-05212384 or the combination

partner (cisplatin) due to toxicity which is specific to either agent, continuation of patient treatment within the study with single agent PF-05212384 or cisplatin will be discussed with the Sponsor on a case-by-case basis.

Figure 8. Amendment 5 Study Design



3.4.1. Dose Rationale

The recommended Phase 2 dose (RP2D) that will be used in the safety and efficacy expansion portion of the study is 180 mg PF-05212384 in combination with cisplatin. The determination of this dose was based on all information related to the overall safety profile, clinical activity, and Principal Investigator input for those patients treated at the MTD.

A total of 33 patients were enrolled in Arm B at doses ranging from 90–310 mg/week in arm (B1–B8). Two DLTs were first observed at the 310 mg dose level (Grade 3 oral mucositis) leading to a dose reduction to 260 mg dose level. Rapid onset oral mucositis was then observed at the 260 mg dose level (not meeting protocol defined DLT criteria). Therefore, the 310 mg and 260 mg levels were deemed unacceptable to move forward due to rapid onset oral mucositis.

Based on safety profile at 310 mg and 260 mg, the dose level selected for additional study in 10 patients was 215 mg. In the 10 patients treated at 215 mg, 6 dose reductions (to 180 mg and one patient then further reduced to 150 mg) were observed in 5 patients during Cycle 1. Five PF-05212384 Cycle 1 dosing visits were missed in 4 patients due to oral mucositis or other significant toxicities.

Based upon this safety profile at the 215 mg dose level, the RP2D was selected as 180 mg IV weekly PF-05212384 in combination with cisplatin (75 mg/mg^2 IV q 3wks).

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria – Original Protocol through Amendment 4

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. Histological or cytological proven diagnosis of advanced solid tumor.
2. For patients enrolled in the dose escalation phase, measurable or evaluable disease as defined by RECIST version 1.1; for patients in the MTD cohorts, measurable disease is required.
3. The following patients will be enrolled:
    a. Arm A: Castrate resistant prostate cancer (CRPC), advanced breast cancer (ABC), or non-small cell lung cancer (NSCLC) that are candidates to treatment with a docetaxel- based combination.
    b. Arm B: Urothelial transitional cell cancer (TCC), triple negative breast cancer (TNBC), NSCLC or ovarian cancer (OC) that are candidates to treatment with a cisplatin- based combination.
    c. Arm C: Her2+ breast cancer (BC) refractory to prior herceptin or lapatinib, Her2+ esophago-gastric cancer, head and neck squamous cell cancer (HNSCC), or NSCLC that are candidates to treatment with a dacomitinib-based combination.
4. Availability of archival tumor biopsy specimens, either formalin-fixed paraffin-embedded (FFPE) tumor tissue block or unstained slides, for biomarker analysis. Patients will need to provide a fresh biopsy if archival material is not available. Patients enrolled in the MTD cohorts must be willing to provide matched fresh tumor biopsies (if clinically feasible) for the pharmacodynamic biomarker studies (See Schedule of Activities, Footnote 23).
5. Age ≥18 years.
6. ECOG Performance Status (PS) must be 0 or 1.
7. Adequate bone marrow function, including:
    a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L.
    b. Platelets ≥100,000/mm3 or ≥100 x 109/L.
    c. Hemoglobin ≥9 g/dL (patients may be transfused to maintain eligibility).

8. Adequate renal function, including:

    a. Arms A and C: Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥50 ml/min as calculated using the method standard for the institution.

    b. Arm B: Serum creatinine ≤1 x ULN and an estimated creatinine clearance ≥60 mL/min.

9. Adequate liver function, including:

    a. Arm A: Total serum bilirubin <1.0 x ULN; Aspartate and Alanine Aminotransferase (AST & ALT) ≤1.5 x ULN; and Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in presence of bone metastases).

    b. Arms B and C: Total serum bilirubin ≤1.5 x ULN; Aspartate and Alanine Aminotransferase (AST & ALT) ≤2.5 x ULN; ≤5.0 x ULN in the presence of hepatic metastases; and Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in presence of bone metastases).

10. Fasting serum glucose ≤126 mg/dL (7.0 mmol/L).

11. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTC AE except for AEs not constituting a safety risk by Investigator judgement or alopecia.

12. Negative serum/urine pregnancy test (for females of childbearing potential) at screening and baseline (within 72 hours of the lead-in dose).

13. Male and female patients of childbearing potential must agree to use two highly effective method of contraception throughout the study and for at least 90 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active.

    Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy.
    - Have medically confirmed ovarian failure or;
    - Achieved post-menopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum FSH level within the laboratory's reference range for postmenopausal females.

14. Evidence of a personally signed and dated informed consent document (ICD) indicating that the patient has been informed of all pertinent aspects of the study.

15. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

4.2. Exclusion Criteria – Original Protocol through Amendment 4

Patients presenting with any of the following will not be included in the study:

1. Patients with known symptomatic brain metastases. 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 the start of study medication, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

2. Chemotherapy, radiotherapy, biologics, or investigational agents within 4 weeks of the lead-in dose (6 weeks for mitomycin C or nitrosoureas). Continued use of luteinizing-hormone-releasing hormone (LHRH) agonists or low dose steroids (<12.5 mg/day of oral prednisone or <2 mg/day dexamethasone) is permitted at the Investigator's discretion for patients with castrate-resistant prostate cancer (CRPC).

3. Major surgery within 4 weeks of baseline disease assessments; or not fully recovered from any side effects of previous procedures.

4. Minor procedures such as lymph node biopsy, needle biopsy, and/or placement of port-a-caths within 1 week of the lead-in dose; or not fully recovered from any side effects of previous procedures.

5. Prior therapy:

    a. >2 prior regimens containing cytotoxic chemotherapy in the metastatic setting.

    b. Prior radiation therapy to >25% bone marrow as estimated by the Investigator.

    c. Arms A: Grade 3 or 4 hypersensitivity reaction associated with prior docetaxel or discontinuation of prior docetaxel due to adverse events.

    d. Arm B: Grade 3 or 4 hypersensitivity reaction associated with prior cisplatin (or other platinum containing compounds) or discontinuation of prior cisplatin due to adverse events.

    e. Arm C: Discontinuation of prior dacomitinib due to adverse events.

6. Concurrent use or anticipated need for medications that are mainly metabolized by UGT1A9 including their administration within 7-days prior to the first dose of study treatment (eg, propofol, propanolol, dapagliflozin, darexaban, mycophenolic acid, and tapentadol).

7. Acetaminophen use within 24 hours of first dose of PF-05212384 (see Section 5.4).

8. Current use or anticipated need for food or drugs that are known strong and/or moderate CYP3A4 inhibitors, including their administration within 7-days prior to the first PF-05212384 dose and during study treatment (ie, 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, and conivaptan; moderate CYP3A4 inhibitors: erythromycin, verapamil, atazanavir, delavirdine, fluconazole, darunavir, diltiazem, imatinib, tofisopam, ciprofloxacin, cimetadine). Aprepitant is classified as a moderate CYP3A4 inhibitor, although it's use is allowed if no suitable alternative can be identified. See Section 5.4.1.

9. Arm C: Current use or anticipated need for food or drugs that are metabolized by CYP2D6, and of narrow therapeutic index including their administration within 10-days prior to the first PF-05212384 dose and during study treatment. See Section 5.4.2 and Appendix 8.

10. Arm C: Current use or anticipated need for proton pump inhibitors and beta blockers.

11. Concurrent administration of herbal preparations.

12. Patients with current or anticipated need for concomitant medications that are known to prolong the QT/QTc interval.

13. 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. Baseline viral assessment is not required in patients with no known infection.

14. Uncontrolled or significant cardiovascular disease:

    a. Known left ventricular ejection fraction (LVEF) <50%.

    b. Myocardial infarction within prior 12 months.

    c. Uncontrolled angina in prior 6 months.

    d. Congestive heart failure in prior 6 months.

    e. Any history or 2nd or 3rd degree heart block unless with current pacemaker.

    f. History or clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes or heart rate <50/minute on pre-entry electrocardiogram (ECG).

g. Prolonged QTc interval at pre-entry ECG. Mean QTc must be ≤450 msec (CTC Grade 1) using Fredericia's correction formula with manual read by Investigator if required.

- The ECG may be repeated for evaluation of eligibility after management of correctable causes for observed QTc prolongation;

h. Hypertension defined as >150/100 that cannot be controlled despite optimal medical therapy.

15. Arm A: Baseline peripheral neuropathy ≥ Grade 2.

16. Arms A: Sensitivity to polysorbate 80.

17. History of interstitial pneumonitis.

18. Arm C: Any clinically significant gastrointestinal abnormalities, which may impair intake, transit or absorption of the study drug, such as the inability to take oral medications in tablet or capsule form and malabsorption syndrome.

19. Pregnant females or breastfeeding females; males and females 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 90 days after last dose of investigational product.

20. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks of the lead-in dose and/or during study participation.

21. 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.

22. 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. Inclusion Criteria – Safety and Efficacy Expansion in patients with TNBC

1. Histological or cytological proven diagnosis of triple negative breast cancer.

- Arm 1: Patients with TNBC with no prior cytotoxic chemotherapy therapy in the metastatic setting;

- Arm 2: Patients with TNBC and one or two prior cytotoxic therapies in the metastatic setting.

2. Measurable disease as defined by RECIST version 1.1.
3. Availability of archival tumor biopsy specimens, either formalin-fixed paraffin-embedded (FFPE) tumor tissue block or unstained slides, for biomarker analysis. Patients will need to provide a fresh biopsy if archival material is not available. Patients enrolled in the MTD cohorts must be willing to provide matched fresh tumor biopsies (if clinically feasible) for the pharmacodynamic biomarker studies (See Schedule of Activities, Footnote 23).
4. Age ≥18 years.
5. ECOG Performance Status (PS) must be 0 or 1.
6. Adequate bone marrow function, including:
   - Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
   - Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
   - Hemoglobin ≥9 g/dL (patients may be transfused to maintain eligibility).
7. Adequate renal function, including:
   - Serum creatinine ≤1 x ULN and an estimated creatinine clearance ≥60 mL/min.
8. Adequate liver function, including:
   - Total serum bilirubin ≤1.5 x ULN; Aspartate and Alanine Aminotransferase (AST & ALT) ≤2.5 x ULN; ≤5.0 x ULN in the presence of hepatic metastases; and Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in presence of bone metastases).
9. Fasting serum glucose ≤126 mg/dL (7.0 mmol/L).
10. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTC AE except for AEs not constituting a safety risk by Investigator judgement or alopecia.
11. Negative serum/urine pregnancy test (for females of childbearing potential) at screening and baseline (within 72 hours of the lead-in dose).
12. Male and female patients of childbearing potential must agree to use two highly effective method of contraception throughout the study and for at least 90 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active.

Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure or;
- Achieved post-menopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum FSH level within the laboratory's reference range for postmenopausal females.

13. Evidence of a personally signed and dated informed consent document (ICD) indicating that the patient has been informed of all pertinent aspects of the study.
14. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

4.4. Exclusion Criteria – Safety and Efficacy Expansion in patients with TNBC

Patients presenting with any of the following will not be included in the study:

1. Patients with known symptomatic brain metastases. 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 the start of study medication, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable. **Consultation with the Sponsor is required prior to screening of patients with previously diagnosed brain metastases.**
2. Chemotherapy, radiotherapy, biologics, or investigational agents within 4 weeks of the lead-in dose (6 weeks for mitomycin C or nitrosoureas).
3. Major surgery within 4 weeks of baseline disease assessments; or not fully recovered from any side effects of previous procedures.
4. Minor procedures such as lymph node biopsy, needle biopsy, and/or placement of port-a-caths within 1 week of the lead-in dose; or not fully recovered from any side effects of previous procedures.
5. Patients with bone-only metastatic disease with no measurable soft tissue component.
6. Prior therapy:
   - Prior platinum (carboplatin or cisplatin) in either the adjuvant or metastatic setting;
   - Prior radiation to >25% bone marrow as estimated by the Investigator.

7. Concurrent use or anticipated need for medications that are mainly metabolized by UDP-glucuronosyltransferase 1-9 (UGT1A9) including their administration within 7-days prior to the first dose of study treatment (eg, propofol, propanolol, dapagliflozin, darexaban, mycophenolic acid, and tapentadol).

8. Acetaminophen use within 24 hours of first dose of PF-05212384 (see Section 5.4).

9. Concurrent administration of herbal preparations.

10. Patients with current or anticipated need for concomitant medications that are known to prolong the QT/QTc interval.

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. Baseline viral assessment is not required in patients with no known infection.

12. Uncontrolled or significant cardiovascular disease:

    - Known left ventricular ejection fraction (LVEF) <50%.
    - Myocardial infarction within prior 12 months.
    - Uncontrolled angina in prior 6 months.
    - Congestive heart failure in prior 6 months.
    - Any history or 2nd or 3rd degree heart block unless with current pacemaker.
    - History or clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes or heart rate <50/minute on pre-entry electrocardiogram (ECG).
    - Prolonged QTc interval at pre-entry ECG. Mean QTc must be ≤450 msec (CTC Grade 1) using Fredericia's correction formula with manual read by Investigator if required.
    - The ECG may be repeated for evaluation of eligibility after management of correctable causes for observed QTc prolongation;
    - Hypertension defined as >150/100 that cannot be controlled despite optimal medical therapy.

13. History of interstitial pneumonitis.

14. Pregnant females or breastfeeding females; males and females 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 90 days after last dose of investigational product.

15. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks of the lead-in dose and/or during study participation.

16. 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.

17. 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.

4.5. Life Style Guidelines

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions should be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity UVb sources such as tanning beds, tanning booths and sunlamps. Patients should be encouraged to apply sunscreen/sunblock daily.

In this study, patients of childbearing potential will receive PF-05212384, a compound for which the teratogenic risk is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for 90 days after the last dose. The investigator or his/her designee, in consultation with the patient, will select two appropriate methods of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in their consistent and correct use. The investigator or his/her designee, at each study visit, will discuss with the patient the need to use highly effective contraception consistently and correctly and document such conversation in the patient chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected.

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:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the patient remains 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, suppository).

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

5. Bilateral tubal ligation or bilateral salpingectomy.

4.6. Sponsor Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the Study Manual.

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 number, contact information for the investigational site and contact details for a help desk 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 patients participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used 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 study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly and if a patient calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

5.1.1. Dose Escalation Portion of B2151002

Following full assessment and determination that the patient meets all eligibility criteria and has given written informed consent for study participation, arm and dose level allocation will be performed by the Sponsor. The Investigator or designee will enroll the patient according to the procedures described in the Study Manual. At the end of the enrollment process, a patient identification number will be assigned, which must be used on all Case Report Form (CRF) pages and on all trial-related documentation and correspondence referencing that patient.

No patient shall receive study drug until the Investigator or designee has received the following information in writing from the Sponsor:

- Confirmation of the patient’s enrolment; and
- Specification of the arm for that patient; and

- Specification of the dose level for that 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.

Eligible patients will be enrolled to receive one of the three study drug treatment regimens in an open-label, unblinded manner. The possible dose levels are displayed in Section 3.1. In Arms A and B, a modified toxicity probability interval (mTPI) method with adjustment based on observed DLT rate will be used to guide the dose assignment (see Section 3.1.1.1). In Arm C, a modified 3+3 design is applied that potentially allows opening of more than one dose level at the same time (see Section 3.1.1.2).

Patients experiencing a DLT may be managed with dose modification or discontinuation. Laboratory values including complete blood count (CBC) and blood chemistry may be obtained within 72 hours of the lead-in dose and Day 1 of every subsequent cycle and reviewed to ensure appropriate values for dosing.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular patient or affect the order in which patients are enrolled.

5.1.2. Safety and Efficacy Expansion in Patients with TNBC

Following full assessment and determination that the patient meets all eligibility criteria and has given written informed consent for study participation, the Investigator or designee will request enrollment to a specific arm based on the patient's prior treatment. Enrollment to a specific arm will be performed by the Sponsor. At the end of the enrollment process, a patient identification number will be assigned, which must be used on all CRF pages and on all trial-related documentation and correspondence referencing that patient.

No patient shall receive study drug until the Investigator or designee has received the following information in writing from the Sponsor:

- confirmation of the patient's enrolment; and
- specification of the arm for that patient; and
- specification of the dose level for that patient.

The Sponsor or designee will inform all sites of enrollment via regular study level communication.

Patients experiencing toxicity may be managed with dose modification or discontinuation. Laboratory values including CBC and blood chemistry may be obtained within 72 hours of Day 1 of every subsequent cycle and reviewed to ensure appropriate values for dosing.

5.2. Drug Supplies

PF-05212384 and dacomitinib are investigational agents and will be supplied free of charge by Pfizer.

Docetaxel and cisplatin are commercially available and will be supplied by the study center (costs will be reimbursed by Pfizer) or by Pfizer.

Study centers will receive a supply of study medication upon activation. The clinical site pharmacy will prepare the study medication supply that is appropriate for the patient on that cycle. Resupplies will be made during the course of the study based on need. The study monitor should be contacted for any issues related to drug supplies.

5.2.1. Formulation and Packaging

5.2.1.1. PF-05212384

PF-05212384 will be supplied as lyophilized powder for infusion and packaged in vials. The vials will be properly labeled according to local regulatory requirements. The details on drug label and supply will be provided in the Investigational Product (IP) Manual.

5.2.1.2. Docetaxel

Docetaxel is commercially available. Central supply or locally obtained commercial supplies of docetaxel will be used. Docetaxel is supplied in single-dose vials containing a sterile solution.

5.2.1.3. Cisplatin

Cisplatin is commercially available. Central supply or locally obtained commercial supplies of cisplatin will be used. Cisplatin is supplied as sterile solution in vials or as a lyophilized powder.

5.2.1.4. Dacomitinib

Dacomitinib will be dispensed in bottles to patients for home dosing as 15 mg tablets for oral administration. The bottles will be properly labeled according to local regulatory requirements. The details on drug label and supply will be provided in the IP Manual.

5.2.2. 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. Dose adjustments or discontinuations should be managed according to the Dose Modification section below. However, per the Investigator's discretion, other dose adjustments may be discussed with the Sponsor.

Any unused product or waste material should be disposed of in accordance with local requirements.

5.2.2.1. PF-05212384

All preparations should take place under aseptic conditions. A pharmacist or pharmacy technician (under the supervision of a pharmacist) will prepare PF-05212384. Specific preparation and dispensing instructions are provided in the IP Manual.

PF-05212384 is known to be incompatible with sodium chloride and care should be taken to avoid contact with saline during both preparation and IV administration.

5.2.2.2. Docetaxel

Docetaxel will be stored, prepared and dispensed according to product labeling.

The total docetaxel dose will be administered on Day 1 of each cycle as a 1-hour infusion.

5.2.2.3. Cisplatin

Cisplatin will be stored, prepared and dispensed according to product labeling.

The total cisplatin dose will be administered on Day 1 of each cycle as a 2-hour infusion. After Cycle 2, cisplatin infusion duration can be modified per institution practices.

5.2.2.4. Dacomitinib

Dacomitinib tablets will be packaged in HDPE bottles, dispensed to patients with adequate supply for the visit schedule, eg, the lead-in period (7 days) or an entire treatment cycle (21 days).

Dacomitinib tablets should be stored according to the product label and kept in their original containers.

5.2.3. Administration

5.2.3.1. PF-05212384

PF-05212384 should be administered weekly as described in the Schedule of Activities as an IV infusion over approximately 30 minutes and as described in the IP Manual. The use of an infusion pump is the preferred method of administration to ensure accurate delivery of the investigational product, but gravity drips are allowed. No premedication is required. In the event of allergic, infusion or hypersensitivity reactions, investigators should institute treatment measures according to best medical and nursing practice and the infusion time can be extended to a maximum of 60 minutes (See Appendix 9).

DO NOT administer any sodium chloride containing solutions or medications concomitantly via the same IV line as PF-05212384. Flush IV lines with 5% Dextrose Injection both before and after PF-05212384 administration.

The possible dose levels for different arms are displayed in Section 3.1.

5.2.3.1.1. Dose Escalation Portion of B2151002

Based on preclinical studies, on Day 1 for Cycles 2 and beyond, patients will receive the companion drug (docetaxel, cisplatin or dacomitinib) first followed by PF-05212384.[15,16] The infusion of PF-05212384 should be initiated approximately 30 minutes following the completion of the docetaxel or cisplatin infusion (Arms A and B) or immediately following the ingestion of the dacomitinib dose (Arm C).

5.2.3.1.2. Retreatment Criteria

PF-05212384 may only be administered on Day 1 of each cycle if all of the following criteria are met based on a blood sample collected within the previous 72 hours:

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

5.2.3.2. Docetaxel

Docetaxel will be administered intravenously at the starting dose of 75 mg/m^2 every 3 weeks. The total docetaxel dose will be administered as a 1-hour IV infusion. The dose of docetaxel will be calculated using body surface area (mg/m^2).

Docetaxel must be used in compliance with its local prescribing information which should be reviewed to ensure that appropriate patients are enrolled in the study.

All patients must receive *prophylactic pre-medication* in order to reduce the incidence and severity of fluid retention and hypersensitivity reactions as per Institution's practices. Suggested pre-medication regimen before each chemotherapy administration consists of oral dexamethasone 8 mg bid or equipotent doses of oral prednisone or prednisolone or methylprednisolone given for 3 days starting 1 day prior to docetaxel administration. Low dose steroids (<12.5 mg/day of oral prednisone or <2 mg/day dexamethasone) are permitted at the Investigator's discretion for patients with CRPC.

5.2.3.2.1. Retreatment Criteria

Docetaxel may only be administered on Day 1 of each cycle if all the following criteria are met based on a blood sample collected within the previous 72 hours:

- Absolute neutrophil count (ANC) ≥1,500/mm^3.
- ALT, AST ≤1.5 x ULN and Alkaline phosphatase ≤2.5x ULN.
- Bilirubin within normal limits (WNL).

5.2.3.3. Cisplatin

Cisplatin will be administered intravenously at the starting dose of 75 mg/m^2 every 3 weeks. The total dose will be administered as a 2-hour IV infusion. The dose of cisplatin will be calculated using body surface area (mg/m^2).

Cisplatin therapy should be immediately preceded and followed by hydration procedures according to the institution's guidelines and administered with appropriate anti-emetics including a $5HT_3$ antagonist.

5.2.3.3.1. Retreatment Criteria

Cisplatin may only be administered on Day 1 of each cycle if all the following criteria are met based on a blood sample collected within the previous 72 hours:

- Absolute neutrophil count (ANC) ≥1,500/mm^3.
- Platelets >75,000/mm^3 ALT, AST ≤1.5 x ULN.
- Serum creatinine ≤1 x ULN and an estimated creatinine clearance ≥60 mL/min.

5.2.3.4. Dacomitinib

Patients will self-administer dacomitinib orally, once daily on a continuous basis. Dacominitib will be supplied as 15 mg tablets and will be taken on an empty stomach (defined as less than 500 calories within 2 hours before or after intake of study medication) and with at least 6 oz (180 mL) of water. Patients will be instructed to record daily administration of the study drugs in a patient diary. Patients will be instructed to swallow study drug tablets whole and not to chew them prior to swallowing. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Patients should be instructed to take their medication at approximately the same time (±3 hours) every day. On days of PK sampling patients will be advised not to take their dose on that day, and bring their medication with them to the clinic. The dose for clinic visit days will be administered after a pre-dose PK sample is drawn.

The possible dose levels of dacomitinib are displayed in Section 5.2.7.4.

Patients will be instructed that if they miss a day's dose, they must not make up the missed dose, but simply resume the dosing schedule the following day. Likewise, patients must be instructed that if they vomit at any time after taking a dose, they must not "make it up" with an extra dose the same day, but resume dosing the next day as prescribed. Similar to all administered doses, any missed or vomited doses must be indicated in the source documents and CRFs.

5.2.4. Medication Errors

Medication errors may result 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 adverse event (AE) page and on the serious adverse event (SAE) form when appropriate. In the event of medication 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 adverse event (AE) page and, if applicable, any associated adverse event(s) are captured on an adverse event (AE) CRF page.

5.2.5. 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 three ways:

- Within a cycle: dose interruption/reduction until adequate recovery during a given treatment cycle.

- Between cycles: next cycle administration may be postponed due to toxicity in the previous cycle.

- In the next cycle: dose reduction based on worst toxicity in the previous cycle.

5.2.6. Dose Interruptions/Delay

PF-05212384: If PF-05212384 treatment is interrupted, the days when treatment is withheld are counted as cycle days and missed doses are skipped. For Arm C, the day treatment is restarted with PF-05212384 will be counted as Day 1 of the next cycle, and the previous cycle is extended accordingly. A treatment delay or interruption of >2 consecutive weeks due to lack of toleration will result in discontinuation of the patient from the study drug, following discussion with the Sponsor. If a patient experiences unacceptable toxicities considered to be related only to PF-05212384 and not to the combination drug (cisplatin, docetaxel, or dacomitinib), continuation of patient treatment within the study with the combination drug (cisplatin, docetaxel, or dacomitinib) as a single agent will be discussed with the Sponsor on a case-by-case basis.

Docetaxel: If toxicities persist and docetaxel cannot be re-administered for >2 weeks after the expected administration of the subsequent cycle (>35 days from the start of docetaxel in the current cycle), the Sponsor should be contacted to discuss treatment continuation. For Arm A, the day treatment is restarted with docetaxel will be counted as Day 1 of the next cycle, and the previous cycle is extended accordingly. If a patient experiences unacceptable toxicities considered to be related only to docetaxel and not to PF-05212384, continuation of patient treatment within the study with PF-05212384 as a single agent will be discussed with the Sponsor on a case-by-case basis.

Cisplatin: If toxicities persist and cisplatin cannot be re-administered for >2 weeks after the expected administration of the subsequent cycle (>35 days from the start of cisplatin in the current cycle), the Sponsor should be contacted to discuss treatment continuation. For Arm B, the day treatment is restarted with cisplatin will be counted as Day 1 of the next cycle, and the previous cycle is extended accordingly. If a patient experiences unacceptable toxicities considered to be related only to cisplatin and not to PF-05212384, continuation of patient treatment within the study with PF-05212384 as a single agent will be discussed with the Sponsor on a case-by-case basis.

Dacomitinib: If dacomitinib treatment is interrupted, the days when treatment is withheld are counted as treatment days and missed doses are skipped. The Sponsor should be contacted to discuss study continuation of the patient. Treatment delay or interruption of >2 consecutive weeks due to lack of toleration will result in discontinuation of the patient from the study drug, following discussion with the Sponsor. If a patient experiences unacceptable toxicities considered to be related only to dacomitinib and not to PF-05212384, continuation of patient treatment within the study with PF-05212384 as a single agent will be discussed with the Sponsor on a case-by-case basis.

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.

5.2.7. Dose Reductions

Following dose interruption or cycle delay due to toxicity, the study drug dose may need to be reduced when treatment is resumed. Dose reductions may be independent for each drug in the combination as suggested by the toxicity profile and the adverse event. After the first cycle, dose reductions may be required based on the worst toxicity experienced in the previous cycle. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed unless discussed with the Sponsor. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed.

Suggested dose reduction criteria are described below for each drug administered in this study. These criteria are provided as guidance only. Decisions on dose reduction and resumption of treatment will be determined according to the judgment of the Investigator.

Arms A and B: Patients experiencing a toxicity that requires dose reduction of PF-05212384, may resume dosing at the next lower dose level of PF-05212384 once adequate recovery is achieved. Chemotherapy (ie, docetaxel and cisplatin) should be maintained at the starting dose unless a chemotherapy-related toxicity mandates a dose reduction. Possible dose levels of PF-05212384 according to study arm are shown in Table 9. Recommended dose reductions for PF-05212384, docetaxel and cisplatin are shown in Table 10, Table 11 and Table 12, respectively.

Arm C: Patients treated at dose level 1 of PF-05212384 experiencing a toxicity that requires dose reduction of PF-05212384 should be withdrawn from treatment unless otherwise agreed between the Investigator and the Sponsor. Patients treated at dose level 1of dacomitinib experiencing a toxicity that requires a dose reduction of dacomitinib may resume dosing at the next lower dose level, once adequate recovery is achieved. Patients treated at subsequent dose levels of PF-05212384 or dacomitinib experiencing a toxicity that requires dose reduction of PF-05212384 or dacomitinib, will have their dose modified once they have adequately recovered from the toxicity. Possible dose levels of PF-05212384 and dacomitinib are shown in Table 9 and Table 13, respectively. Recommended dose reductions for PF-05212384 and dacomitinib are shown in Table 10 and Table 14, respectively.

If a patient has a dose reduction for a drug-related toxicity, the dose will not be re-escalated.

5.2.7.1. PF-05212384

Possible dose levels of PF-05212384 according to study arm are shown in Table 9.

In Arms A and B, patients treated at dose level 1 of PF-05212384 experiencing a toxicity in Cycle 1 that requires dose reduction, will receive a reduced dose of PF-05212384 to 75 mg/wk for Cycle 2 onwards.

In Arm C, patients treated at dose level 1 of PF-05212384 experiencing a toxicity during Cycle 1 that requires dose reduction of PF-05212384, should be withdrawn from treatment unless otherwise agreed between the Investigator and the Sponsor.

Table 9. Possible Dose Levels of PF-05212384

	PF-05212384 mg/wk	
Dose Level	**Arms A & B**	**Arm C**
(-1)	75	----
1#	90	90
2	110	110
3	130	130
4	150	150
5	180	180
6	215	215
7	260	260
8	310	310

starting dose

Guidelines for dose modification of toxicities considered related to PF-05212384 are shown in Table 10.

Table 10. PF-05212384 - Dose Modification Guidelines for Related Toxicities

Worst Toxicity (CTCAE v.4.03)	PF-05212384
Hematologic toxicities:	
• Grade 4 neutropenia ≥7 days • Febrile neutropenia (defined as neutropenia Grade ≥3 and a single body temperature >38.3°C or a sustained temperature of ≥38°C for more than one hour) • Neutropenic infection (defined as Grade 3 or 4 neutropenia with Grade ≥3 infection) • Grade 3 thrombocytopenia with bleeding • Grade 4 thrombocytopenia	• Withhold dose until toxicity is Grade ≤2, then resume treatment at 1 lower dose level. • If the toxicity reoccurs, withhold dose until toxicity is Grade ≤2, and then resume treatment at the next lower dose level or discontinue treatment at the discretion of the Investigator.
Non-Hematologic Toxicities	
Non-Hematologic toxicities not highlighted below:	
• Grade 1 or Grade 2	• Continue at same dose level.
• Grade 3 or 4	• Withhold dose until toxicity is Grade ≤2, then resume treatment at 1 lower dose level. • If the toxicity reoccurs with Grade 3 or 4 severity, withhold dose until toxicity is Grade ≤2, and then resume treatment at the next lower dose level or discontinue treatment at the discretion of the Investigator.
Gastrointestinal toxicities	
• Grade 1 or Grade 2	• Continue at same dose level.
• Grade ≥3 nausea/vomiting despite optimal antiemetic treatment • Grade ≥3 diarrhea despite optimal anti- diarrheal treatment	• Withhold dose until toxicity is Grade ≤2, then resume treatment at 1 lower dose level. • If the toxicity reoccurs with Grade 3 or Grade 4 severity, despite optimal supportive care, withhold dose until toxicity is Grade ≤2 and then resume treatment at the next lower dose level or discontinue treatment at the discretion of the Investigator.
Metabolic toxicities	
• Grade 1	• Continue at the same dose level.
• Grade ≥2 hyperglycemia	• Implement hyperglycemia management as described in Appendix 5.
• Grade 4 hyperglycemia despite optimal anti-hyperglycemic treatment	• Discontinue treatment.
Skin toxicities	
• Grade 1 and Grade 2	• Continue at the same dose level. • Implement skin rash management as described in Appendix 6.
• Grade 3 and Grade 4	• Implement skin rash management as described in Appendix 6 and withhold dose until toxicity is Grade ≤1; resume treatment at 1 lower dose level. • If the toxicity reoccurs to Grade 3 or 4 despite dose reduction, discontinue treatment.

Worst Toxicity (CTCAE v.4.03)	PF-05212384
Pulmonary toxicity (pneumonitis)	
• Grade 1	• Continue at the same dose level.
• Grade 2	• Withhold dose until toxicity is Grade ≤1, then resume treatment at 1 lower dose level.
• Grade 3 and 4	• Discontinue treatment.
Failure to recover Failure to recover to Grade ≤1 or baseline severity for drug-related toxicity (or, at the Investigator's discretion, Grade ≤2 for toxicities not considered a safety risk for the patient) after delaying the initiation of the next cycle by a maximum of 2 weeks	• Discontinue treatment.

5.2.7.2. Docetaxel

The docetaxel dose may be reduced to 60 mg/m^2 for Cycle 2 onwards depending on individual tolerability. The minimum dose acceptable for docetaxel will be 60 mg/m^2. Guidelines for dose modification of docetaxel are shown in Table 11. For the management of docetaxel related toxicities and for retreatment criteria at the start of each cycle, refer to the product label.

The use of hematopoietic growth factors (eg, G-CSF) for the treatment of febrile neutropenia will be permitted for Cycle 1 onwards and to support neutrophil counts for Cycles 2 onwards, according to local guidelines. In the absence of local guidelines, the ASCO guidelines 2006 should be followed.[37]

Table 11. Docetaxel - Dose Modification Guidelines for Related Toxicities for a New Cycle Based on Worst Toxicity Observed in the Prior Cycle

Worst Toxicity (CTCAE v.4.03) in Prior Cycle	Docetaxel Dose (mg/m^2)
Hematologic toxicities (1)	
• Grade 4 neutropenia ≥7 days	60
• Febrile neutropenia (defined as neutropenia Grade ≥3 and a single body temperature >38.3°C or a sustained temperature of ≥38°C for more than one hour)	60
• Neutropenic infection (defined as Grade 3 or 4 neutropenia with Grade ≥3 infection)	60
Non-Hematologic toxicities	
Non-Hematologic toxicities not highlighted below:	
Grade 3	60
Grade 4	Permanently Discontinue
Gastrointestinal toxicities (1)	
• Persistent Grade ≥3 diarrhea despite maximal antidiarrheal therapy	60
Persistent Grade ≥3 nausea despite maximal medical therapy	60
Persistent Grade ≥3 vomiting despite maximal antiemetic therapy	60
Grade ≥3 stomatitis	60
Hepatic toxicities	
Bilirubin >ULN (1,2)	60
ALT or AST >1.5 ULN (1,2)	60
AP >2.5 ULN (1,2)	60
ALT and/or AST >3.5 ULN concomitant with AP >6-ULN	Permanently Discontinue
Other Docetaxel-specific toxicities	
Skin toxicities	
Grade 3 skin toxicity (1)	60
Grade 4 skin toxicity	Permanently Discontinue
Neuropathy	
Grade 3 peripheral (sensory) neuropathy (1)	60
Grade 4 peripheral neuropathy	Permanently Discontinue
Grade ≥3 peripheral motor neuropathy	Permanently Discontinue
Hypersensitivity reaction	
Grade ≥3 hypersensitivity reaction (3)	Permanently Discontinue

1 If symptoms persist with dosage adjusted, docetaxel should be discontinued.
2 If abnormal values recover (ie, bilirubin ≤ULN; AST or ALT ≤1.5xULN; AP ≤2.5xULN) within the duration of the cycle + a maximum of 2 weeks, re-treat at 1 dose level reduction. If abnormal values do not recover, discontinue treatment with docetaxel.
3 Severe hypersensitivity reactions consist often in severe hypotension, bronchospasm or generalized rash/erythema.

5.2.7.3. Cisplatin

The cisplatin dose may be reduced to 60 mg/m^2 (approximately 75% of starting dose) and 40 mg/m^2 (approximately 50% of starting dose) for Cycles 2 onwards depending on individual tolerability. Guidelines for dose modification of cisplatin are shown in Table 12. For the management of cisplatin related toxicities and for retreatment criteria at the start of each cycle, refer to the product label.

The use of hematopoietic growth factors (eg, G-CSF) for the treatment of febrile neutropenia will be permitted for Cycle 1 onwards and to support neutrophil counts for Cycles 2 onwards, according to local guidelines. In the absence of local guidelines, the ASCO guidelines 2006 should be followed.[37]

Table 12. Cisplatin - Dose Modification Guidelines for Related Toxicities for a New Cycle Based on Worst Toxicity Observed in Prior Cycle

Worst Toxicity (CTCAE v.4.03) in Prior Cycle	Cisplatin Dose (mg/m^2)
Hematologic toxicities (1)	
• Febrile neutropenia (defined as neutropenia ≥ Grade 3 and a single body temperature >38.3°C or a sustained temperature of ≥38°C for more than one hour)	60
• Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding	60
Non-Hematologic toxicities	
Non-Hematologic toxicities not highlight below:	
• Any Grade 3 toxicity	60
• Any Grade 4 toxicity	40 or discontinue (3)
Gastrointestinal toxicities (1,2)	
• Grade 3 nausea or vomiting despite optimal antiemetic prophylaxis and therapy	60
• Grade 4 vomiting despite optimal antiemetic prophylaxis and therapy	40
Neurologic toxicities	
Peripheral neurotoxicity	
• Grade 2 (1)	40 or discontinue at Investigator's discretion
• Grade 3 (1)	40 when recovered to Grade 2 or discontinue at Investigator's discretion
• Grade 4	Permanently Discontinue
Ototoxicity (Tinnitus or significant hearing loss)	40 or discontinue at Investigator's discretion
Renal toxicities	
Creatinine Clearance (Calculated or Measured)	
• <60 mL/min (1)	40
• <45 mL/min	Delay for maximum of 4 weeks. If not recovered adequately for re-treatment discontinue

(1) If symptoms persist with dosage adjusted, cisplatin should be discontinued.
(2) Use of antiemetic supportive care is mandatory, as per local practices.
(3) Investigator discretion based on the type of toxicity seen and which course is medically most sound.

5.2.7.4. Dacomitinib

As shown in Table 13, the dacomitinib dose may be reduced for Cycle 2 onwards depending on individual tolerability. The minimum acceptable dose for dacomitinib will be 15 mg QD.

Table 13. Possible Dose Levels for Dacomitinib

Dose Level	Dacomitinib (mg QD PO)
-1	15
1#	30
2	45

starting dose

Guidelines for dose modification of dacomitinib are shown in Table 14.

Table 14. Dacomitinib - Dose Modifications Guidelines for Related Toxicities Based on Worst Toxicity Observed

Worst Toxicity (CTCAE v.4.03) in Prior Cycle	Dacomitinib
Hematologic and Non-Hematologic toxicities	
Grade 1 or Grade 2	• Continue at same dose level. Implement adverse event management guidelines as described in Appendix 7.
Grade 3 or intolerable Grade 2	• Interrupt treatment. • Upon recovery to Grade 1 or baseline, resume treatment at same dose level or reduce the dose to the next lower dose level at the discretion of the Investigator.
Grade 4	• Interrupt treatment. • Upon recovery to Grade 1 or baseline, reduce the dose to the next lower dose level or discontinue treatment at the discretion of the Investigator.

5.2.8. Compliance

5.2.8.1. PF-05212384, Docetaxel, and Cisplatin

The site will complete 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 Pfizer monitor.

5.2.8.2. Dacomitinib

Patients will maintain diaries to include missed or changed doses, or significantly delayed doses (ie, >6 hours from intended dosing time). Patients will be required to return all unused study medication at the beginning of each cycle. The number of tablets returned by the patient will be counted, documented and recorded by site personnel. All empty, partially empty and un-used bottles should be returned to the site for drug accountability purposes and held at the site until monitored.

The Investigator and study team will also evaluate patient compliance with the study regimen. Potential reasons for non-compliant dosing (ie, AEs, lost medication) will be followed up by the study site personnel and strategies to improve dosing compliance will be explored.

5.3. Drug Storage and Drug Accountability

The Investigator, or an approved representative (eg, pharmacist), will ensure that all trial drug is stored in a secured area, under recommended storage conditions on the product labels, and in accordance with applicable regulatory requirements. Under no circumstances should the Investigator or other site personnel supply trial drug to other Investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from Pfizer. Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms (eg, NCI form). In either case, the forms must identify the investigational product, including batch numbers, and account for its disposition on a patient by patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Pfizer.

Adequate records documenting receipts, use, return, loss, or other disposition of study drugs must be kept. Study drug (vials and tablets) must be used according to the protocol directions. The reason for missed doses should be entered on the Case Report Form. To ensure adequate records, all trial drug supplies will be accounted for in the case report form and drug accountability inventory forms as instructed by Pfizer. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused by the patients must be returned to Pfizer or its appointed agent (eg, CRO). If Pfizer authorizes destruction at the trial 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. Destruction must be adequately documented.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported to the sponsor.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product.

Storage conditions stated in the SRSD (ie, Investigator Brochure [IB], Core Data Sheet [CDS], United States Package Insert [USPI], Summary of Product Characteristics [SPC], or Local Product Document [LPD] may be superseded by the label storage.

5.3.1. PF-05212384

PF-05212384 should be stored as indicated in its original labeled carton, per the labeled storage conditions. The product label will supersede any instructions in the IB for PF-05212384. If the investigational product does not appear to be visually appropriate (eg, broken vial), it should not be administered and the Sponsor should be contacted immediately for further instruction.

5.3.2. Docetaxel and Cisplatin

Docetaxel and cisplatin storage conditions are described in the product label for each drug.

5.3.3. Dacomitinib

Dacomitinib tablets should be stored as indicated, according to the labeled storage conditions (which may supersede any instructions in the IB for dacomitinib). Patients should be instructed to keep their medication in its original container.

5.4. Concomitant Medication(s)

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.[37] All concomitant medications and blood products, as well as interventions (eg, analgesic use, paracentesis, etc) received by patients from screening until the End of Treatment visit will be recorded on the CRF.

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted but they may be used to treat treatment-emergent neutropenia as indicated by the current ASCO guidelines.

Patients currently being treated with bisphosphonates may continue treatment as long as the treatment has been initiated before the first dose of study drug. Initiation of bisphosphonate therapy after randomization will be considered progression of disease unless otherwise agreed by the Investigator in consultation with the Sponsor.

Patients on warfarin should be carefully monitored when study drug is initiated and patients on study drug should have frequent PT and INR monitoring should anticoagulation with warfarin be initiated.

Additionally for over the counter pain or fever management, if no alternative non-steriodal anti-inflammatory drugs (NSAIDs) are viable, acetaminophen may be used but should be discontinued 24 hours prior to administration of PF-05212384. It can be re-initiated 24 hours after the end of PF-05212384 infusion.

Patients should avoid concomitant medications that are known to prolong QT/QTc interval.

The docetaxel and cisplatin product labels should be consulted for any restrictions that may apply for concomitant medications.

5.4.1. Drugs Interacting with CYP3A4

In all treatment arms, patients should avoid the use of strong and moderate CYP3A4 inhibitors as well as strong CYP3A4 inducers.

Because inhibition of CYP3A4 isoenzymes may increase study drug exposure leading to a potential increase in toxicities, the use of known strong 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, imatinib, tofisopam, ciprofloxacin, cimetidine)[38] are not permitted from 7-days prior to the first dose of study drug until study treatment discontinuation. Aprepitant is classified as a moderate CYP3A4 inhibitor, although use is allowed if no suitable alternative can be identified.

Study drug metabolism may be induced when taking strong CYP3A4 inducers (eg, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St. John's Wort) resulting in reduced plasma concentrations. Therefore co-administration of study drug in combination with these and other strong CYP3A4 inducers is not permitted from 7-days prior to the first dose of PF-05212384 until study treatment discontinuation.

5.4.2. CYP2D6 Substrates (Arm C only)

Dacomitinib inhibited CYP2D6 activity in vitro with an IC50 of 0.063 μM (~30 ng/mL). Drug-drug interaction of dacomitinib with substrates of CYP2D6 could occur depending on the systemic concentrations of dacomitinib achieved in the clinical study and dependence of the CYP2D6 substrate on 2D6 for metabolism. Therefore drugs dependent on CYP2D6 metabolism with narrow therapeutic index eg, procainamide, pimozide and thioridazine are prohibited in combination with dacomitinib.

The use of drugs that are highly dependent on CYP2D6 for metabolism requires consideration of both the therapeutic index and the degree of CYP2D6 metabolism. Substitution within the therapeutic class is recommended if possible, otherwise the directions below should be followed.

- For drugs that are highly dependent on CYP2D6 metabolism: dose reduction should be based on substrate sensitivity to CYP2D6 metabolism. As a guidance, a starting dose reduction of 75% (25% of the dose given without co-administration with dacomitinib) should be considered and close clinical monitoring is required.

- For drugs that are partly dependent on CYP2D6-mediated metabolism, there is a high likelihood of supra-therapeutic exposure in combination with dacomitinib. No dose reduction is required when starting dacomitinib, but clinical monitoring is required; based on the patient's response, dose reductions may be necessary.

- Pro-drugs, or drugs with highly active metabolites such as codeine and tramadol, should be replaced with an alternative within the therapeutic class as conversion to the pharmacologically active moiety is CYP2D6 metabolism-dependent and their exposure with the co-administration of dacomitinib may be sub-therapeutic. Opiates such as morphine, hydromorphone, oxymorphone and oxycodone can be used as substitutes to replace codeine or tramadol for analgesia.

Appendix 8 provides a comprehensive list of CYP2D6 substrates coded according to the therapeutic index and the degree of CYP2D6 metabolism. This is not an all inclusive list. If there is uncertainty whether a concomitant medication is contraindicated, the Investigator should contact the Sponsor study team.

5.4.3. P-glycoprotein Substrates (Arm C only)

Concurrent administration of drugs which are P-glycoprotein (P-gp) substrates and have a narrow therapeutic index (eg, digoxin) should be monitored for exaggerated effect and/or toxicities.

5.4.4. Strong Amines (Arm C only)

Lidocaine exposures may significantly increase in the presence of strong amines, such as dacomitinib. Lidocaine may be used systemically but clinical monitoring (including telemetry) is recommended.[36]

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

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

Low dose steroids (<12.5 mg/day of oral prednisone or <2 mg/day dexamethasone) or luteinizing-hormone-releasing hormone (LHRH) agonists may be used at the Investigator's discretion for patients with CRPC on Arm A.

5.4.6. Supportive Care

Palliative radiotherapy is permitted for the treatment of painful bony lesions providing the lesions were known to be present 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 the investigational agents PF-05212384 and dacomitinib with radiotherapy, study drug treatment should be interrupted during palliative radiotherapy, stopping 5 days before and resuming treatment after recovery of any radiotherapy-related toxicity to baseline.

Medication intended solely for supportive care (eg, analgesics, antidepressants) may be used at the Investigator's discretion.

5.4.7. Hematopoietic Growth Factors

The use of hematopoietic growth factors (eg, G-CSF) for the treatment of febrile neutropenia will be permitted for Cycle 1 onwards and to support neutrophil counts for Cycles 2 onwards, according to local guidelines. In the absence of local guidelines, the ASCO guidelines 2006 should be followed.[37]

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

5.4.8. Corticosteroids

Chronic, systemic high-dose treatment with corticosteroids (prednisone ≥12.5 mg/day or dexamethasone ≥2 mg/day) should be avoided with the exception of Arm A. Treatment with docetaxel requires mandatory prophylactic pre-medication with corticosteroids. Also, low dose steroids (<12.5 mg/day of oral prednisone or <2 mg/day dexamethasone) may be used at the Investigator's discretion for patients with CRPC on Arm A.

Steroids for the acute treatment of skin rash or respiratory toxicity are allowed.

5.4.9. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and study treatment required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping study treatment is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate study treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.4.10. Oral Mucositis – Prophylaxis and Management

Oral mucositis was observed in 50% of patients treated in the PF-05212384/cisplatin combination. The Sponsor highly recommends one or more of the following strategies for prevention of oral mucositis. These strategies are outlined below and are recommended to begin pre-dose on Cycle 1 Day 1 and continued as clinically indicated.

Patients who have not had a dental checkup within 6 months prior to start of dosing are encouraged to do so, especially to identify any persistent issue related to recent chemotherapy. Once on treatment, patients are to consult the site health care team prior to undertaking any dental or oral surgery procedure to determine if it would be appropriate to proceed depending on presence of any ongoing oral mucosal inflammation.

To decrease the rate and severity of oral mucositis, the patient should perform a steroid containing "swish-and-spit" regimen eg., dexamethasone 0.5 mg/5 ml swish and expectorate, four times daily. The daily number of steroid containing mouth rinses can be reduced as clinically indicated.

Topical anesthetics or systemic analgesics may be used as indicated in judgment of the Investigator and according to local clinical practices.

Patients should practice good oral care including a soft-bristle toothbrush replaced frequently and use of bland rinses or moisturizers. Also, frequent sips of water during meals may assist swallowing and therefore maintain caloric intake and hydration in patients experiencing oral pain.

Use of chlorhexidine is to be avoided.

Between scheduled visits, patient self-report of oral mucosal discomfort or of visible changes in appearance to oral mucosa is encouraged. Periodic systematic examination of the oral cavity is required at scheduled visits and as otherwise indicated by patient self-report between visits.

Consultation with nutritionist is to be considered if toxicity may compromise maintenance of adequate caloric intake.

6. STUDY PROCEDURES

All patients being considered for the trial must sign an informed consent for the trial prior to any trial specific procedures. Trial procedures are described in the Section 7 and in the Schedule of Activities. Safety laboratory tests (hematology, blood chemistry, urinalysis, coagulation) and tumor assessments may be done up to 72 hours prior to scheduled Day 1 visit on any cycle to facilitate availability of results to the Investigator at the time of clinic visit.

Other tests and/or increased frequency of examinations or clinical follow up may be needed for patient management depending on findings emerging from the study. The results of these additional tests or examinations will be recorded on the CRF.

6.1. Screening

All patients being considered for the trial and eligible for screening must sign an informed consent form prior to performing any trial related procedures that are not standard of care. The Investigator, or a person designated by the Investigator, will explain the benefits and risks of participation in the trial to each patient, patient's legal representative or impartial witness, and obtain written informed consent prior to the patient entering the trial (before initiation of non-routine tests and administration of trial drug).

The final ICD must be agreed to by Pfizer and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in language readily understood by the patient. The Investigator will retain each patient's original consent form, signed and dated by the patient or by the patient's legal representative, and by the person who conducted the informed consent discussion.

This protocol requires clinical visits and evaluations to determine eligibility prior to trial enrollment and the first dose of study drug (See Schedule of activities and its footnotes). Required screening and baseline laboratory evaluations are summarized in Section 7.1.3. Patients will be assigned individual trial identification numbers at the time they are approved and registered for enrollment.

Baseline assessments must be performed within 28 days (unless otherwise specified) prior to commencing study treatment, as outlined on the schedule of activities. Baseline tumor biopsy samples may be archival (see Schedule of Activities, Footnote 23) and if the patient has consented to a fresh tumor biopsy, this must be performed within 28 days prior to the start of study treatment. Study treatment start is considered 7 days prior to Cycle 1 Day 1 (Arms A and B) or 14 days prior to Cycle 1 Day 1 (Arm C).

As part of the screening/baseline assessment, all patients will undergo a complete medical history, including ongoing concomitant medications, clinical assessments (including vital signs, height, body weight, ECOG performance status, baseline signs and symptoms, and triplicate 12-lead resting ECG), MUGA or ECHO (Arm C patients), and tumor assessments.

Documentation of tumor history (Primary Diagnosis) should include histological or cytological classification, stage information, treatment history (surgery, systemic treatment and radiotherapy) as well as duration and best response to immediate prior regimen, tumor grade, histologic subtype, and relevant tumor-specific molecular markers, if available (eg, PI3K/mTOR/Akt pathway alteration [*PIK3CA* mutation, PTEN loss] *KRAS, BRAF, HER2* or *EGFR* gene expression and/or mutation status). In addition, information regarding the sample type for the initial diagnostic biopsy will be collected.

The required baseline laboratory tests include: blood hematology and chemistry, HbA1c, pregnancy test (serum or urine), and urinalysis.

Consent will be required for all patients enrolling in this study to access archived tumor biopsies to examine variation in proteins and genes associated with PI3K, HER-family receptor and MAPK signaling; examples include PTEN and *PIK3CA*, *PIK3R1*, *AKT, KRAS*, and *BRAF*. If an archived biopsy is not available, a fresh biopsy sample at baseline will be required. Paired tumor biopsies are also required from patients treated in the MTD cohorts (see Section 7.3).

Following completion of the screening assessments and confirmation of eligibility, patients may be enrolled.

For screening procedures see Schedule of Activities and Section 7.

6.2. Study Period

For treatment period procedures, see Schedule of Activities and Section 7.

6.3. Follow-up Visit

For follow-up procedures see Schedule of Activities and Section 7.

6.4. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time 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 according to RECIST;
- Global deterioration of health status requiring discontinuation;

- Adverse event;
- QTc prolongation of >500 msec or 60 msec over baseline;
- Pregnancy;
- 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.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further 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.

If the study is prematurely terminated for reasons other than safety, the Sponsor will make reasonable efforts, in accordance with applicable local regulatory requirements and laws, to provide PF-05212384 and/or dacomitinib to patients deriving therapeutic benefit, for as long as appropriate drug supplies are available and, for patients treated in this study, until the treatment is authorized and commercially available for this use.

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 which he/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 Assessments

Safety assessments will include collection of AEs, SAEs, vital signs, physical examination, ECG (12-lead), left ventricular ejection fraction (LVEF) measurements, and laboratory assessments including pregnancy tests. In addition, the use of concurrent medications will be determined.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy; once at the start of Screening and once at the baseline visit, within 72 hours of study treatment start. A negative pregnancy result is required 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 therapy and additionally whenever one 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 study medication but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by IRB/IECs 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.

Baseline signs and symptoms will be recorded at baseline and then reported as adverse events during the study if they worsen in severity or increase in frequency.

7.1.3. Laboratory Safety Assessments

Blood for hematology and chemistry will be drawn prior to the administration of study treatment at the time points described in the Schedule of Activities and analyzed at local laboratories.

Investigators may have additional blood tests performed for the purpose of planning treatment administration, dose modification, or following AEs.

Table 15. List of Laboratory Test Assessments

Hematology	**Chemistry**		**Urinalysis**
Hemoglobin	ALT (SGPT)	BUN or Urea	Urine dipstick for urine protein: If ≥2+ protein on urine dipstick, then collect spot urine sample to calculate urine protein to creatinine ratio.
Platelets	AST (SGOT)	Serum Creatinine	Urine dipstick for urine blood : If positive perform a microscopic analysis (Reflex Testing)
WBC	Alk Phos	Uric Acid	
Absolute Neutrophils	Sodium	Glucose (fasted)*	**Pregnancy Test**
Absolute Lymphocytes	Potassium	Insulin	For female patients of childbearing potential, serum or urine
Absolute Monocytes	Magnesium	HbA1c	
Absolute Eosinophils	Chloride	Albumin	**Coagulation**
Absolute Basophils	Calcium	Total Protein	INR
	Lactate dehydrogenase	Phosphorus	PTT
	Total Bilirubin		
* It is recommended that patients be under fasting conditions (no food or drink within 8 hours) for all blood chemistry panels on Day 1 of each cycle.			

7.1.4. Vital Signs and Physical Examination

Patients will have a physical exam to include an examination of major body systems and an assessment for emergent toxicities or changes from prior visits, weight, vital signs (blood pressure and heart rate 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 baseline only. Complete physical examinations will be conducted by a physician, trained physician's assistant, or nurse practitioner, as acceptable according to local regulation.

7.1.5. (12-Lead) ECG

Triplicate 12-lead electrocardiogram (ECG) (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), three consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTc interval. If the mean QTc is prolonged (≥501 msec, ie, ≥ CTC AE 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 QTc of ≥501 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed.

In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 501 msec. If QTc interval reverts to less than 501 msec, and in the judgment of Investigator(s) and Sponsor is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring. If QTc interval >500 msec or an increase of >60 msec is considered to be related to study therapy, the patient will be discontinued from the study.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, 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 a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG should be obtained at the time of the event. Also, additional triplicate ECGs may be performed as clinically indicated.

When matched with PK sampling, the ECG should be collected prior to the scheduled PK draw; the timing of the PK collection over rides the timing for the ECG collection (ie, if a PK sample is scheduled at 1 hour post dose and an ECG is scheduled 1 hour post dose, then the ECGs should be collected just prior to the 1 hour PK collection, and the PK sample should be collected at the nominal time).

7.1.6. Left Ventricular Ejection Fraction Measurements (Arm C only)

Determination of LVEF by either MUGA scan or ECHO will be measured at baseline, the end of Cycle 3, the end of Cycle 6, and then every 6 cycles for Arm C patients only. The same technique should be used throughout for an individual patient.

If an absolute decrease in LVEF of >20% is noted, by either MUGA or ECHO, then the LVEF will be repeated as soon as feasible using the alternate radiologic method (if available); if the decrease is verified further, cardiac evaluation will be undertaken per the judgment of Investigator. In the absence of clinical signs and symptoms of left ventricular dysfunction or LVEF <40%, treatment may continue if judgment of the Investigator is that patient may benefit from ongoing therapy. Any clinically significant changes will be recorded as adverse events and further evaluated as clinically warranted at the discretion of the Investigator.

For any patient discontinuing therapy for signs or symptoms suggestive of left ventricular dysfunction, continued evaluation of LVEF at about 3-4 month interval to assess for resolution is recommended.

7.2. Pharmacokinetics Assessments

Blood samples (3 mL whole blood per sample collection timepoint) will be collected for PK analysis of PF-05212384, docetaxel, and dacomitinib (and the desmethyl metabolite PF-05199265) as outlined in the Schedule of Activities. A blood sample of 6 mL of whole blood per sample collection timepoint, will be collected for the PK analysis of cisplatin as outlined in the Schedule of Activities. Blood samples for PK assessment will be collected up through Cycle 6. PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, when feasible, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs which are suspected to be related to study drug treatment and the date and time documented in the CRF.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection 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 clinical Investigators, patient, and Sponsor.

PK samples will be assayed for PF-05212384, docetaxel, cisplatin and dacomitinib (and its metabolite PF-05199265) using validated analytical methods in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Study Manual.

As part of understanding the pharmacokinetics of the study drugs, samples may be used for future metabolite identification and/or further evaluation of the bioanalytical methods. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not processed during the course of these experiments, will be discarded.

7.2.1. Pharmacokinetic Assessments in the Safety and Efficacy Expansion in TNBC

Blood samples (3 mL whole blood per sample collection timepoint) will be collected for PK analysis of PF-05212384 as outlined in the Schedule of Activities. Blood samples for PK assessment will be collected up through Cycle 6. PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, when feasible, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs which are suspected to be related to study drug treatment and the date and time documented in the CRF.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection 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 clinical Investigators, patient, and Sponsor.

PK samples will be assayed for PF-05212384 using validated analytical methods in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Laboratory Manual.

As part of understanding the pharmacokinetics of the study drugs, samples may be used for future metabolite identification and/or further evaluation of the bioanalytical methods. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not processed during the course of these experiments, will be discarded.

7.3. Pharmacodynamic Assessments

CCI [redacted]

Biomarker assessments are described below in more detail, however additional markers may be included as pre-clinical studies or literature reports further elucidate the mechanism of action of any of the investigational products. Details on preparation and handling of all biomarker samples including processing, storage, and shipment will be provided in the Laboratory Manual. The source of the samples is listed below in Table 16. Please also refer to the Schedule of Activities and the Laboratory Manual for details pertaining to specific days of sample collection and sample preparation.

CCI [redacted]

7.3.1. Tumor Biopsy

Acquisition of the mandatory archival FFPE tumor tissue block or unstained slides representing primary or metastatic tumor tissue are required and may be completed prior to the 28 day screening window, but it is required for patient enrollment. Note that if archival FFPE tumor tissue cannot be provided, a fresh biopsy is required. Patients may not be enrolled into the study without providing either an archived or fresh tumor sample. For the tumor sample, paraffin blocks are preferred, but freshly cut slides will be accepted. At least twenty unstained, 5-micron slides prepared from the paraffin block must be provided. Sample will be analyzed for genetic markers indicative of drug sensitivity (eg, PIK3CA, BRCA1, other).

This study is designed to utilize phosphoproteomics techniques to evaluate signaling pathways that could be modified in vivo by the drugs used in this study. The biomarker studies will be used to help understand the in vivo mechanism of action of the agents, levels of pathway blockade in response to treatment, and potential mechanisms of resistance owing to the inherent plasticity in cancer cell signaling pathways.

To meet this goal, biopsies obtained pre- and post-study treatment (ie, "paired" or "matched" fresh tumor biopsies) will be requested from all patients including the dose escalation and the MTD cohorts. The paired tumor core biopsy are mandatory for patients enrolled in the MTD cohorts unless the Investigator considers it to pose a safety risk to the patient; in this case, a discussion between the Investigator and Sponsor should take place before a final decision is made. Examples of safety risks may include, but are not limited to pulmonary metastases deep within the thoracic cavity with high probability of bleeding or lung injury or liver metastases located within the liver posing a high risk of bleeding if biopsied. Biopsies obtained pre- and post-study treatment will be requested from all patients in the expansion portion of the study enrolling patients with TNBC.

Biopsies will be obtained at screening and after drug administration as indicated in the Schedule of Activities. A formalin fixed paraffin block will be prepared and collected from each biopsy. These paired samples will be analyzed predominantly for phosphoprotein biomarkers indicative of pathway modulation, or for genetic markers correlated to drug sensitivity (eg, emerging *KRAS* mutation). Additional markers may be included as pre-clinical studies or literature reports further elucidate the mechanisms of action of any of the study drugs. CCI [redacted]

Details on preparation handling of these samples including processing, storage, and shipment will be provided in the Laboratory Manual.

7.3.2. Whole Blood/Plasma Biospecimens

Whole blood biospecimens will be collected pre dose on Cycle 1 Day 1 and Cycle 2 Day 15 post-dose, but no more than 72 hours later). Baseline biospecimens will be utilized for circulating tumor cell and germline BRCA analysis. Peripheral blood mononuclear cells (PBMCs) or platelets from whole blood will be isolated for analysis of surrogate protein markers for drug sensitivity using reverse phase protein array (RPPA) analysis.

CCI [redacted]

7.3.3. Effect of PI3K Inhibition on Glucose Metabolism

A PI3K/mTOR inhibitor should disrupt the cellular uptake and metabolism of glucose. In the Phase 1 studies, administration of PF-05212384 resulted in increased levels of circulating glucose, insulin, and c-peptide within one week of therapy, as well as increased levels of glycosylated hemoglobin (HbA1c) after about one month of therapy. These observations suggest that gedatolisib can block the PI3K/mTOR signaling in humans and that blood based biomarkers can be utilized as pharmacodynamics biomarkers. The current studies will therefore employ metabolic biomarkers such as glucose, insulin, c-peptide and HbA1c as pharmacodynamics markers for dual PI3K/mTOR inhibition.

7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging must include the chest (chest x-ray or high resolution CT) at baseline and at all subsequent cycles in order to monitor for pulmonary effects of the study drug PF-05212384 and to monitor target or non-target lesions in the chest. Imaging should include abdomen and pelvis CT or MRI scans if disease is being followed in these areas. A brain CT or MRI scan for patients with known or suspected brain metastases and bone scan and/or bone x-rays for patients with known or suspected bone metastases are required.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule of Events, whenever disease progression is suspected (eg, symptomatic deterioration), and at the End of Treatment visit (if not done in the previous 6 weeks). Patients who have had a tumor assessment as standard of care within 28 days of the lead-in dose but prior to signing the ICD will not need to have a re-assessment solely for the purposes of the study, as long as the appropriate data is available for entry onto the study CRF.

Assessment of response will be made using RECIST version 1.1 (Appendix 2).

All patients' files and radiologic images must be available for source verification and for potential peer review.

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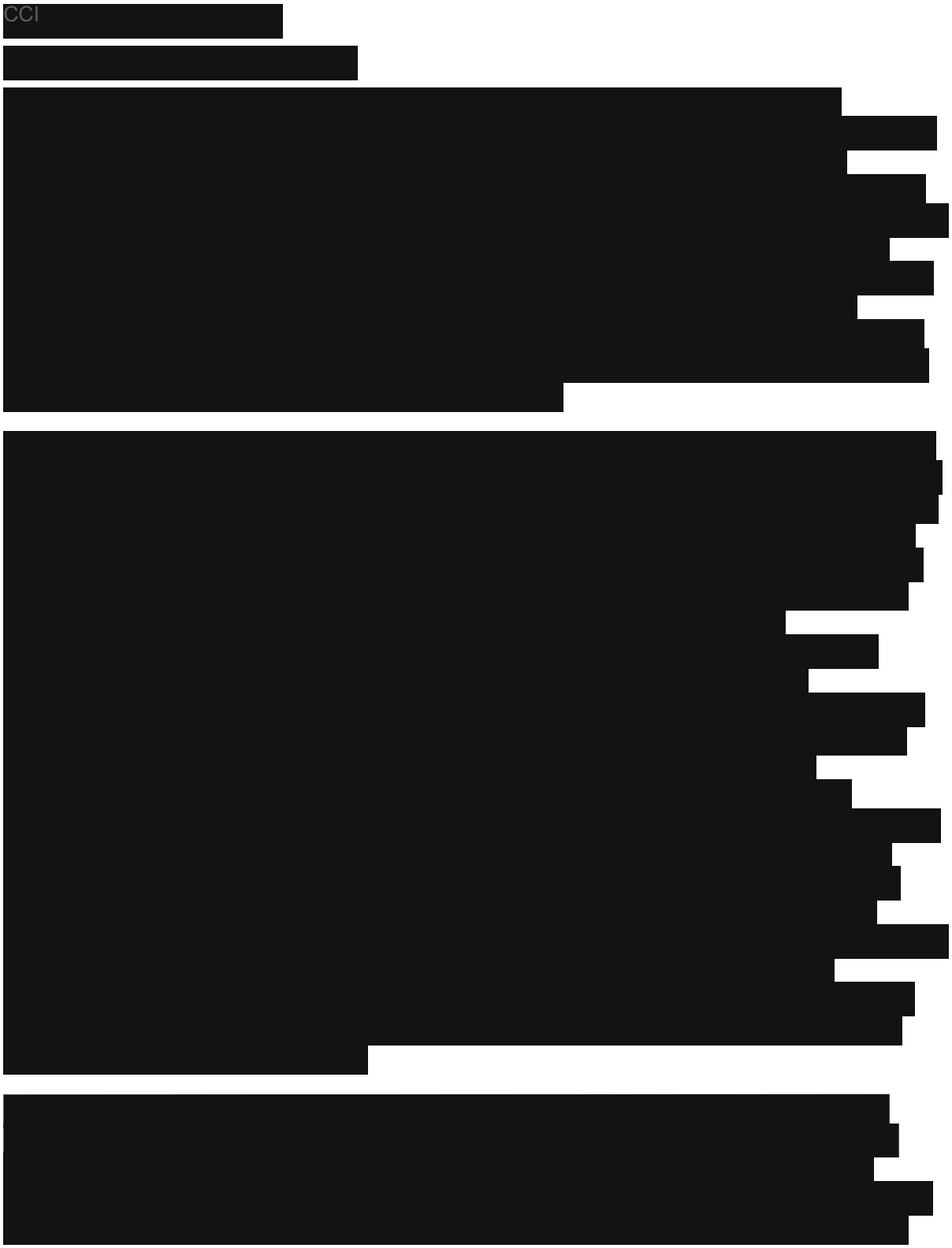

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7.6. Patient Reported Outcomes in the Safety and Efficacy Expansion in TNBC

Patient reported outcomes of health-related quality of life and breast cancer specific disease/treatment related symptoms will be assessed using European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) and the corresponding module for breast cancer (EORTC QLQ-BR23) (Appendix 10 and Appendix 11 respectively). Patients will complete each instrument at pre-dose on Day 1 and Day 8 of Cycle 1 and 2, on Day 1 of each subsequent cycle starting with Cycle 3 and at the end of treatment visit. Completed questionnaires are always considered source document and must be filed accordingly.

Patients must complete these instruments in clinic (cannot be taken home) and prior to having any tests and to any discussion of their progress with the physician or clinic personnel at the site. Interviewer administration in clinic may be used under special circumstances (eg, patient forgot their glasses or feels too ill). The instruments will be given to the patient in the appropriate language for the site.

7.6.1. EORTC QLQ-C30 and EORTC QLQ-BR23

The EORTC QLQ-C30 (Version 3.0) and the QLQ-BR23 module (Appendix 10 and Appendix 11, respectively) were selected for inclusion in the study as they are responsive to clinical status and change over time and are also the two most commonly used patient reported measures in breast cancer clinical studies.[47] Both self report measures are also widely recognized as clinically valid and reliable measures for assessing global QOL, disease symptoms, and treatment related symptoms in breast cancer patients.

The EORTC QLQ-C30 (see Appendix 10) consists of 30 questions which are incorporated into five multi-item functional domains (physical, role, cognitive, emotional, and social domains); a global health status/ global quality of life (QOL) scale; three multi-item symptom scales (fatigue, pain, nausea and vomiting scales); and six single items that assess additional cancer-related symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and the perceived financial burden of treatment. The questionnaire employs 28 4-point Likert scales with responses from "not at all" to "very much" and two 7-point Likert scales for global health and overall QOL.[48] For functional and global QOL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale using standard scoring algorithm.[49] For symptom-oriented scales, a higher score represents more severe symptoms.

The EORTC QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC QLQ-C30 and consists of two functional scales (body image and sexuality); three symptom subscales (arm/hand, breast, and systemic side effects) and single items covering sexual enjoyment, distress at hair loss, and future perspective.

Both the EORTC QLQ-C30 and the QLQ-BR-23 module require about 15 minutes to complete and are available in many languages.

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 a serious adverse event (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 adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as a 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. Serious adverse events 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 serious adverse events 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 one 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;
- Extravasation;
- 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. 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 (outside of protocol-stipulated dose adjustments) 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.

8.5. 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 Common Toxicity Criteria for Adverse Events (CTCAE) Grade 5 (see 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.

8.5.1. 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 Section 8.13.1 SAE Reporting Requirements).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Liver Function Tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an Investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a patient, such LFT results should be handled and followed up as described below.

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 (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above.

- For patients with pre-existing AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 X ULN, or ≥8 X 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 one time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (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 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.

8.6. 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 work-up 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;
- Pre-planned 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 non-invasive 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.

8.7. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 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.

8.8. 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 serious adverse 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 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 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.

8.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) 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 a Serious Adverse Event (SAE) Report Form and Exposure in Utero (EIU) 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 EIU 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 it's outcome for all EIU 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 EIU 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 exposure during pregnancy 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.

8.10. 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 adverse event.

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 subject 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.

8.11. Withdrawal Due to Adverse Events (See also Section 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.

8.12. 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.

8.13. 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.

8.13.1. 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 timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports

as well as to the initial and follow-up reporting of exposure during pregnancy, 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 timeframes 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.

8.13.2. 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.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer. 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.

9.1. Analysis Sets

1. Safety analysis set.
    - The safety analysis set includes all enrolled patients who receive at least one dose of study medication.
2. Full analysis set.
    - The full analysis set includes all enrolled patients.

3. Per protocol analysis set (evaluable for DLT).

    - The per protocol analysis set includes all enrolled patients who receive at least one dose of study medication and who do not have major treatment deviations during the first cycle. Patients with major treatment deviations in Cycle 1 are not evaluable for DLT and may be replaced. Major deviations include:

    - Administration of less than 75% of the planned Cycle 1 dose of either treatment in the combination (provided that the reduction is not due to toxicity attributable to both agents in the combination).

    - Administration of more than 125% of the planned Cycle 1 dose of either treatment in the combination.

4. PK analysis sets.

    - The PK parameter analysis set is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest.

    - Patients with a change to the planned PF-05212384 30 minute infusion time (eg, increasing to 60 minutes), will not be included in the summary statistics for PK parameters and will be listed separately.

5. Biomarker Analysis sets

    - Molecular profiling tumor analysis set: is defined as all enrolled patients who start treatment and have a baseline archived tumor biopsy FFPE sample (or fresh FFPE if archived is not available) successfully analyzed for at least one of the selected biomarkers.

    - Expression tumor analysis set: is defined as all enrolled patients who start treatment and have both baseline and on-treatment optional fresh FFPE tumor biopsy samples successfully analyzed for at least one of the selected biomarkers.

    - Serum PD analysis set: is defined as all enrolled patients who start treatment and have a baseline and at least one post-baseline measurement for at least one serum PD biomarker.

6. Response Analysis set

    - All enrolled patients who receive at least one dose of study medication, have the disease under study, and an adequate baseline tumor assessment.

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Arms A and B

The MTD estimation in Arms A and B employs the mTPI method with adjustment of dose assignment criteria based on observed DLT rate.[28,34] The mTPI method is a Bayesian method with only one assumption about the dose-toxicity relationship, which is, toxicity increases as dose increases. The most important parameter of the mTPI design is the target DLT rate at the MTD, which is 25% for this study. An interval for DLT rate, called equivalence interval, is also required for the mTPI method. Any DLT rate in the equivalence interval is considered sufficiently close to the target DLT rate for the purpose of MTD estimation. In this study, the equivalence interval is 20%-32%. For each dose level, the uniform prior is assumed for the DLT rate.

Dose assignment recommendations are based on the posterior distribution of the DLT rate. Specifically, the DLT rate on (0, 1) is divided into three intervals: the equivalence interval, the interval below it, and the interval above it. Unit probability mass (UPM) is calculated for each of these intervals based on the posterior distribution of the DLT rate. The mTPI method recommends a higher dose level to the next cohort of patients if the interval below the equivalence interval has the highest UPM at the current dose level; and it recommends a lower dose level to the next cohort of patients if the interval above the equivalence interval has the highest UPM at the current dose level. To protect patients from highly toxic dose levels, a dose level is considered unacceptably toxic and eliminated from further testing, if the posterior probability is 95% or higher that its DLT rate is above the target DLT rate, provided that 3 or more patients have been treated at the dose level. In addition, if the total number of patients treated at the current dose level is at least 5, then the criteria for recommending dose escalation and de-escalation will be adjusted based on the observed DLT rate at the current dose level: if it is above 32%, then dose de-escalation will be recommended; if it is below 20%, then dose escalation will be recommended, subject to the feasibility of the dose so recommended. The use of observed DLT rate for dose assignment is similar to an approach used by the local optimal interval design.[34] The dose assignment recommendations for cumulative number of patients in the range of 3-15 are presented in Figure 7.

At the end of dose finding, the MTD will be estimated based on isotonic regression. Specifically, the MTD estimate will be selected from the dose levels whose isotonic estimates of DLT rates are less than or equal to 32%, and it will be the dose level for which the isotonic estimate of the DLT rate is closest to the target DLT rate. If two or more dose levels share the same isotonic estimate of DLT rate, the MTD estimate will be the highest dose level in the case that the isotonic estimate is lower than the target DLT rate; and the lowest dose level in the case that the isotonic estimate is greater than the target DLT rate.

Simulations of multiple scenarios for the proposed MTD finding method will be described and summarized in the Statistical Analysis Plan (SAP).

If 9 or more patients have been treated cumulatively at any dose level and the observed DLT rate exceeds 40% among them, then enrollment will be stopped for the affected dose level, pending review of the data by the Sponsor and Investigators.

9.2.2. Statistical Method for Arm C

For Arm C, a zone-based design will be employed for MTD estimation.[35] This is a 3+3 design modified for 2-dimensional MTD finding. The rule of dose assignment is described in Section 3.1.1.

Table 17 shows the probability of escalating to the next dose level for a range of underlying true DLT rates. For example, for a dose level at which a DLT occurs in 10% of patients, there is a greater than 90% probability of escalating. Conversely, for a dose level at which a DLT occurs with a rate of 70%, the probability of escalating is 3%. It is assumed that dose escalation occurs with either 0/3 or 1/6 patients experiencing DLTs.

Table 17. Probability of Escalating Dose Level

True underlying DLT rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalating dose level	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.009	0.001

If the observed DLT rate exceeds 40% among all patients treated at the MTD (including those in the dose-escalation cohorts and expansion cohort), then enrollment will be stopped for the affected dose level, pending review of the data by the Sponsor and Investigators.

9.2.3. Statistical Method for the Safety and Efficacy Expansion Arm 1 and 2

The expansions will confirm the safety and tolerability of the dose selected as the RP2D during the dose escalation while also assessing the anti-tumor activity of PF-05212384 plus cisplatin in patients with TNBC.

Enrollment of patients to a specific arm may be discontinued if no or minimal anti-tumor activity in that arm is observed during the study.

9.3. Sample Size Determination

On April 1, 2015, Pfizer Inc. decided to stop enrolment in Arms A and C of the B2151002 clinical trial. Patients previously identified for enrolment in Arm A and C were permitted to enter the study after notification of the decision. Due to closure, the MTD of those combinations will not be established. All references to objectives, endpoints, study design, assessments, etc. and analysis of data in Arm A and C will be limited to the number of patients treated up to the enrolment discontinuation date for each Arm (June 10, 2015 for Arm A and 06 July 2015 for Arm C). The decision is based on the company's change in prioritization for the portfolio and is not due to any safety/efficacy concerns or regulatory interactions.

There are 3 arms in the dose escalation portion of the study. For each arm, the primary objective is to estimate the MTD.

For Arms A and B, the dose escalation is with respect to PF-05212384 only. A total of 21 patients were enrolled in Arm A and approximately 40 are expected to be enrolled in Arm B. The sample size for Arm B will vary depending on the number of DLTs observed.

It is expected that approximately 40 patients will be needed, however, due to the number of DLTs this may vary.

For Arm C, there were 2 components prior to the April 1, 2015 decision. In the first component, patients participated in a dose escalation phase aimed at estimating the MTD. The study did not proceed to the second component and a total of 33 patients were enrolled.

Sample Size Determination for the Safety and Efficacy Expansion in TNBC

The TNBC expansion portion of the study will enroll 30 response-evaluable patients, including 15 in Arm 1 and 2, respectively, to estimate the objective response rate (complete response (CR)+partial response (PR)).

- For 1st line patients (Arm 1):
    - Posterior Bayesian probabilities will be used to assess the probabilities of anti-tumor activity. For example, using a non-informative Jeffrey's prior, a 60% response rate (confirmed overall response rate (ORR): CR+PR) (9 out of 15 patients) would have a posterior probability equal to 88% that the true response is not inferior to 45%.
- For 2nd/3rd-line patients (Arm 2)
    - Posterior Bayesian probabilities will be used to assess the probabilities of anti-tumor activity. For example, using a non-informative Jeffrey's prior, a 40% response rate (confirmed ORR: CR+PR) (6 out of 15 patients) would have a posterior probability equal to 91% that the true response is not inferior to 25%.

The total sample size for the study is approximately 124 patients.

9.4. Efficacy Analysis

9.4.1. Efficacy Analysis for the Dose Escalation

In the dose escalation portion of the study, anti-tumor activity is a secondary objective.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, tumor type, starting dose, tumor response at each visit, and best overall response. In addition, dates of progression, death, first response and last tumor assessment will be listed.

If the data permits, objective response rate and clinical benefit response rate will be provided by arm and by tumor type. Objective response includes CR and PR. Clinical benefit response includes PR, CR and SD (≥24 weeks from the first dose to treatment failure).

9.4.2. Efficacy Analysis for the Safety and Efficacy Expansion in TNBC

In the expansion portion of the study, objective response is the primary endpoint. Objective response rate, clinical benefit response rate, duration of response (DOR), and PFS will be calculated for expansion Arm 1 and 2. Objective response includes CR and PR. Clinical benefit response (CBR) includes CR, PR and SD (≥24 weeks from first dose to treatment failure).

DOR is calculated from first date of PR or CR to the date of progression or death due to any cause. In the event of no progression or death, the last tumor assessment date without progression will be used in this calculation.

PFS is defined as the time from first dose to date of first documentation of progression or death due to any cause. Details of censoring for PFS will be provided in the SAP.

The posterior probabilities used to assess the probabilities of anti-tumor activity will be calculated based on the final number of responders and response-evaluable patients.

Tumor response will be presented in the form of patient data listings that include, but are not limited to, starting dose, tumor response at each visit, and best overall response. In addition, dates of progression, death, first response, and last tumor assessment will be listed.

9.5. Analysis of Other Endpoints

9.5.1. Analysis of Single- and Multiple-Dose Pharmacokinetics

Plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC_{last}, AUC_{τ}) for PF-05212384, docetaxel, cisplatin and dacomitinib will be estimated using non-compartmental analysis. If data permit or if considered appropriate, area under the plasma concentration versus time curve to infinity (AUC_{inf}), terminal elimination half-life ($t_{½}$), plasma clearance (CL), apparent volume of distribution V_d, accumulation ratio (R_{ac}) and linearity ratio (R_{ss}) will also be estimated. The single dose and steady-state PK parameters will be summarized descriptively by dose, cycle and day.

For PF-05212384, docetaxel, cisplatin and dacomitinib concentrations will be summarized descriptively (n, mean, SD, percent coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day (single dose and steady-state) using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

The observed accumulation ratio and the linearity ratio will be summarized descriptively. Each will be analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation and linearity ratios for each dose.

Trough concentrations will be plotted for each dose using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.

9.5.1.1. Metabolite Profiling

Plasma metabolite profiling will be summarized in a separate report and not included in the clinical study report (CSR).

9.5.2. Statistical Analysis of Biomarkers

For biopsy samples, summary statistics (eg, the mean and standard deviation, median, CV, and minimum/maximum levels of continuous, and frequency and percentages of categorical biomarker measures) will be determined at baseline and post-treatment for each arm. For each pair of specimens, the ratio-to-baseline of these same parameters will also be calculated.

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

9.6. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the safety analysis set.

9.6.1. Analysis of Primary Endpoint

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation portion of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in Section 3.3. The number of patients with DLTs will be listed by dosing cohort as well as by dose level for each arm. Adverse Events constituting DLTs will be listed per dose level by arm.

9.6.2. Analysis of Secondary Safety Endpoints

9.6.2.1. 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, which will be by arm, will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. 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 (Lead-in, Cycle 1 and Cycles beyond 1).

9.6.2.2. Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay by arm. The analyses will summarize laboratory tests both on the entire study period and by cycle (Lead-in, Cycle 1 and Cycles beyond 1).

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

9.6.2.3. Electrocardiogram Assessments

The analysis of ECG results will be based on patients in the safety analysis set who have both baseline 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 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, Fredericia's and possibly other factors). The adequacy of the correction method may be assessed graphically (plots of QT and QTc versus RR) and supplementary transformations may be considered, as appropriate. Data will be summarized and listed for QT, HR, RR, PR, QRS, and QTcF by arm, dose, and time. 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 baseline QTc values and changes from baseline in QTc by arm, dose, and time point. For each patient and by arm, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Categorical analysis of the QTc data will be conducted on maximum change from baseline in QTc and maximum post-baseline QTc.

Shift tables will be provided for baseline vs. worst on treatment QTc using the maximum CTC AE Grade. Shift tables will also be provided for ECG abnormality on treatment vs baseline (yes, no, not done: (n, %)). The effect of drug concentrations on QTc interval changes from baseline will be explored graphically. Additional concentration-QTc analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.7. Patient Reported Outcomes

The number and percentage of patients who complete the EORTC QLQ-C30 and QLQ-BR23 will be summarized in a table, as will the reasons for non-completion of these measures.

The mean change of absolute global QOL scores from baseline (and 95% CI) will be calculated. Repeated measures mixed model analyses will also be conducted to estimate changes in scores over time. The number and proportion of patients who improved, worsened, or remained stable for all of the symptom and functional domains, global QOL,

and single items of the QLQ-C30 and the QLQ-BR23 will be summarized in a table. Analyses will be performed to determine if the change from baseline scores achieve the appropriate minimally important difference (MID) cut-off for the scale being examined.

In addition to the above analyses, an examination of the time to deterioration (TTD) for global QOL will be carried out using survival analysis methods.

9.8. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the study. 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. This will include surveillance for SAEs according to regulatory guidelines.

Discussions between the Investigators and the Sponsor regarding AEs and laboratory test abnormalities seen at each dose level will occur in an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and determine if further patient enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits 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 is 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.

The study site may be subject to review by the Institutional Review Board (IRB)/IEC, 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.

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 Records

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 is true. Any corrections to entries made in the CRFs, 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 Investigator's 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, telephone calls reports). The records should be retained by the Investigator according to International Conference on Harmonisation (ICH), 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 (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC 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, 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 on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used during the informed consent process must be reviewed by the Sponsor, approved by both the IRB/IEC and available for inspection.

The Investigator must ensure that each study patient, or his/her legal representative, 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 or the patient's legal representative 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 IEC and Investigator databases may be used as recruitment procedures.

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 which 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 is defined as the time at which it is deemed that sufficient 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 other Participating Countries

The End of Trial in all participating countries is defined as the Last Patient Last Visit (LPLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-05212384 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 a 4 week time period. 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 Trial 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 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 pre-specified 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 has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) 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, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. 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, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Fruman, D.A., R.E. Meyers, and L.C. Cantley, *Phosphoinositide Kinases.* Annual Review of Biochemistry, 1998. **67**(1): p. 481-507.

2. Vivanco, I. and C.L. Sawyers, *The phosphatidylinositol 3-Kinase-AKT pathway in human cancer.* Nat Rev Cancer, 2002. **2**(7): p. 489-501.

3. Vara, J.A.F., et al., *PI3K/Akt signalling pathway and cancer.* Cancer Treatment Reviews, 2004. **30**(2): p. 193-204.

4. Prenen, H., S. Tejpar, and E.V. Cutsem, *New Strategies for Treatment of KRAS Mutant Metastatic Colorectal Cancer.* Clinical Cancer Research, 2010. **16**(11): p. 2921-2926.

5. Tabernero, J., et al., Dose- and Schedule-Dependent Inhibition of the Mammalian Target of Rapamycin Pathway With Everolimus: A Phase I Tumor Pharmacodynamic Study in Patients With Advanced Solid Tumors. J Clin Oncol, 2008: p. JCO.2007.14.5482.

6. Chan, S., Targeting the mammalian target of rapamycin (mTOR): a new approach to treating cancer. Br J Cancer, 2004. **91**(8): p. 1420-1424.

7. Sarbassov, D.D., et al., Phosphorylation and Regulation of Akt/PKB by the Rictor-mTOR Complex. Science, 2005. **307**(5712): p. 1098-1101.

8. Gross ME, Shazer RL, Agus DB. Targeting the HER-kinase axis in cancer. Semin Oncol, 2004;**1** (suppl): 9-20.

9. Barnes CJ, Kumar R. Epidermal growth factor receptor family tyrosine kinases as signal integrators and therapeutic targets. Cancer Metastasis Rev., 2003;**22**(4):301-307.

10. Albanell J, Codony J, Rovira A, Mellado B, Gascon P. Mechanism of action of anti-HER2 monoclonal antibodies: scientific update on trastuzumab and 2C4. Adv Exp Med Biol. 2003;**532**:253-268.

11. Arteaga C. Targeting HER1/EGFR: a molecular approach to cancer therapy. Semin Oncol. 2003;**30(3 Suppl 7)**:3-14.

12. Slamon DJ, et. al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;**344**:783-792.

13. Paez et. al., EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;**304**:1458-1461.

14. Lynch TJ et. al., Activiating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. N Engl J Med. 2004;**350**:2129-2139.

15. Fekete M, Santiskulvong C, Eng C, Dorigo O. Effect of PI3K/Akt pathway inhibition-mediated G_1 arrest on chemosensitization in ovarian cancer cells. Anticancer Res. 2012;32:445-452.

16. Wallin JJ, Giam J, Prior WW, Lee LB, Berry L, Belmont LD, Koeppen H, Belvin M, Friedman LS, Sampath D. GDC-0941, a novel class I selective PI3K inhibitor, enhances the efficacy of docetaxel in human breast cancer models by increasing cell death in vitro and in vivo. Clin Cancer Res. 2012;18:3901-3911.

17. Carden CP, Stewart A, Thavasu P, Kipps E, Pope L, Crespo M, Miranda S, Attard G, Garrett MD, Clarke PA, Workman P, de Bono JS, Gore M, Kay SB, Banerji U. The association of PI3 kinase signaling and chemoresistance in advanced ovarian cancer. Mol Cancer Ther. 2012;**11**:1609-1617.

18. Shi Y, Chen L, Li J, Lv YL, Sun Q, Wang LX, Jiao SC. Prognostic and predictive values of pERK1/2 and pAkt-1 expression in non-small cell lung cancer patients treated with adjuvant chemotherapy. Tumor Biol. 2011;**32**:381-390.

19. Morishita N, Tsukahara H, Chayama K, Ishida T, Washio K, Miyamura T, Yamashita N, Oda M, Morishima T. Activation of Akt is associated with poor prognosis and chemotherapeutic resistance in pediatric B-precursor acute lymphoblastic leukemia. Pediatr Blood Cancer. 2012;**59**:83-89.

20. Donev IS, Wang W, Yamada T, Li Q, Takeuchi S, Matsumoto K, Yamori T, Nishioka Y, Sone S, Yano S. Transient PI3K inhibition induces apoptosis and overcomes HGF-mediated resistance to EGFR-TKIs in EGFR mutant lung cancer. Clin Cancer Res. 2011;**17(8)**:2260-2269.

21. Lee J, Lyndsay H. Antimitotic Agents (Chapter 25, Section 8) in Devita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 8th Edition. Editors: Devita V, Hellman S, Rosenberg SA. Lippincott, Williams & Wilkins, Philadelphia, PA. 2008.

22. Wallin JJ, Guan J, Prior W-W, Edgar KA, Kassees R, Sampath D, Belvin M, Friedman LS. Nuclear phosphor-Akt increase predicts synergy of PI3K inhibition and doxorubicin in breast and ovarian cancer. Sci Transl Med. 2010;**2**(48):1-8.

23. Xu R, Nakano K, Iwasaki H, Kumagai M, Wakabayashi R, Yamasaki A, Suzuki H, Mibu R, Onishi H, Katano M. Dual blockade of phosphatidylinositol 3'-kinase and mitogen-activated protein kinase pathways overcomes paclitaxel-resistance in colorectal cancer. Cancer Letters. 2011;**306**:151-160.

24. Andre F, and Zielinski CC. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. Ann Oncol 2012;23;vi46-vi51.

25. Shi J, Yao D, Liu W, Wang N, Lv H, Zhang G, Ji M, Xu L, He N, Shi B, Hou P. Highly frequent PIK3A amplification is associated with poor prognosis in gastric cancer. BM Cancer. 2012;**12**:50-61.

26. Tanaka K, Babic I, Nathanson D, Akhavan D, Guo D, Gini B, Dang J, Zhu S, Yang H, De Jesus J, Amzajerdi AN, Zhang Y, Dibble CC, Dan H, Rinkenbaugh A, Yong WH, Vinters HV, Gera JF, Cavenee WK, Cloughesy TF, Mannin BD, Baldwin AS, Mischel PS. Oncogenic EGFR signaling activates an mTORC2-NF-κB pathway that promotes chemotherapy resistance. Cancer Discovery. 2011;**1**:524-538.

27. Mallon R, Feldberg LR, Lucas J, Chaudhary I, Dehnhardt C, Santos ED, Chen Z, dos Santos O, Kaloustian A, Venkatesan A, Hollander I. Antitumor efficacy of PKI-587, a highly potent dual PI3K/mTOR kinase inhibitor. Clin Cancer Res. 2011 17:3193-3203.

28. Package Insert: Taxotere®. http:www.taxotere.com.

29. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szcze A¸ Fidias P, Millward M, Belani CP. Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non–Small-Cell Lung Cancer: The TAX 326 Study Group. JCO 2003; 21:3016-3024.

30. Manegold C, van Zandwijk N, Szczesna A, Zatloukal P, Au JSK, Blasinska-Morawiec M, Serwatowski P, Krzakowski M, Jassem J, Tan EH, Benner RJ, Ingrosso A, Meech SJ, Readett D, Thatcher N. A phase III randomized study of gemcitabine and cisplatin with or without PF-3512676 (TLR9 agonist) as first-line treatment of advanced non-small-cell lung cancer. Ann Oncology 2012;23:72-77.

31. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis O-F, Simms L, Sugarman KP, Gandara D. Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naïve Patients With Advanced-Stage Non–Small-Cell Lung Cancer. JCO 2008;26:3542-3551.

32. Janne PA, Boss DS, Camidge DR, Britten CD, Engelman JA, Garon EB, Guo F, Wong S, Liang J, Letrent S, Millham R, Taylor I, Eckhardt SG, Schellens JHM. Phase I Dose-Escalation Study of the Pan-HER Inhibitor, PF299804, in Patients with Advanced Malignant Solid Tumors. Clin Cancer *Res* 2011;17:1131-1139.

33. Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin. Trials. 2010;7(6):653-663.

34. Liu S, Yuan Y. Optimal interval designs for Phase 1 clinical trials. Statistics in Medicine. 2012. revised.

35. Huang, X, Biswas, S, Oki, Y et al: A Parallel Phase I/II Clinical Trial Design for Combination Therapies. Biometrics 63, 429–436, June 2007.

36. Guidance for Industry. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs. U.S Department of Health and Human Services FDA, Center for Drug Evaluation and Research (CDER), October 2005.

37. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. JCO 2006; 24: 3187-3205.

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

39. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med 2010. 36: 1938-1948.

40. Hudis CA, Gianni L. Triple-negative breast cancer: An unmet medical need. The Oncologist 2011; 16: 1- 11. Doi: 10.1634/theoncologist.2011-S1-01.

41. Carey LA, Rugo HS, Marcom PK, Mayer EL, Esteva FJ…Winer EP. TBCRC 001: randomized phase II study of cetuximab in combination with carboplatin in stage IV triple-negative breast cancer. J Clin Oncol 2012. 30: 2615-2623.

42. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Breast Cancer. Version 2.2016. NCCN.org. Downloaded from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

43. Sirohi B, Arnedos M, Popat S, Ashley S, Nerukar A…Smith IE. Platinum-based chemotherapy in triple-negative breast cancer. Ann Oncol 2008. doi: 10.1093/annonc/mdn395 First published online: June 20, 2008.

44. Narod SA, Dent RA, Foulkes WD. CCR 20th Anniversary Commentary: triple-negative breast cancer in 2015—still in the ballpark. Doi: 10.1158/1078-0432. CCR-14-3122.

45. Baselga J, Gomez P, Greil R, Braga S, Climent MA…Awada A. Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. J Clin Oncol 2013; 31: 2586-2592.

46. Gordon V, Banerji S. Molecular Pathways: PI3K pathway targets in triple-negative breast cancer. Clin Cancer Res 2013; 19: 3738-44. Doi: 10.1158/1078-0432.CCR-12-0274.

47. Krohe et al. Patient-Reported Outcomes in Metastatic Breast Cancer: AReview of Industry-Sponsored Clinical Trials. *Breast Cancer: Basic and Clinical Research* 2016:10 93–102 doi:10.4137/BCBCR.S39385.

48. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365–376.

49. Fayers PM, Aaronson NK, Bjordal K et al. EORTC QLQ-C30 Scoring Manual, 3rd edition. Brussels: European Organisation for Research and Treatment of Cancer 2001.

50. Uhm JE, Park YH, Yi SY, et al. Treatment outcomes and clinicopathologic characteristics of triple-negative breast cancer patients who received platinum-containing chemotherapy. Int J Cancer 2009; 124, 1457-1462.

51. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 2.2016. NCCN.org.

Appendix 1. Abbreviations

ABC	Advanced Breast Cancer
AE	Adverse Event
AIDS	Aquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferases
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferases
ATP	Adenose Triphosphate
AUC	Area Under the Curve
AUC inf	Area under the plasma concentration-time profie from time zero to infinity
BAD	BCL-2 Associated Cell Death
BC	Breast Cancer
BID	Bis In Die (twice daily)
BRCA	Breast Cancer
BRCA1	Breast Cancer 1
BRCA2	Breast Cancer 2
BSA	Body Surface Area
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{ave}	Average plasma/serum concentration
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CDS	Core Data Sheet
CI	Confidence Interval
CL	Plasma clearance
C_{max}	Maximum Observed Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CRC	Colorectal Cancer
CRM	Continuous Reassessment Method
CRO	Clinical Research Organization
CRPC	Castrate Resistant Prostate Cancer
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events, version 4.0
C_{trough}	Observed concentration at end of dosing interval
CV	Percent Coefficient of Variation

DAI	Dosage Administration Instructions
DLT	Dose Limiting Toxicity
CCI	[redacted]
DOR	Duration of Response
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
EGFR	Epidermal Growth Factor Receptor
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EORTC QLQ-BR23	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Companion Module
EIU	Exposure In Utero
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FDAAA	US Food and Drug Administration Amendments Act
FFPE	Formalin Fixed Paraffin Embedded
FIH	First In Human
FOX-O	Forkhead Box O Protein
GBM	Glioblastoma Multiforme
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
H&E	Hematoxylin and eosin
HbA1c	Hemoglobin A1c; Glycosylated hemoglobin
HBV	Hepatitis B
HCV	Hepatitis C
HER	Human Epidermal Growth Factor Receptor
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Heart rate
HRD	Homologous Recombination Deficiency
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous

LFT	Liver Function Test
LHRH	Luteinizing-hormone-releasing hormone
LPD	Local Product Document
LPLV	Last Patient Last Visit
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
Ms	Milliseconds
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
mTOR	Mammalian Target of Rapamycin
MID	Minimally Important Difference
MUGA	Multi-gated Radionucleoide Study
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAIDs	Non-steriodal anti-inflammatory drugs
NSCLC	Non Small Cell Lung Cancer
OC	Ovarian Cancer
OR	Overall Response
ORR	Overall Response Rate
PARP	Poly (ADP-Ribose) Polymerase
PBMC	Peripheral Blood Mononuclear Cell
PCD	Primary Completion Date
PD	Progressive Disease (when in reference to tumor assessments)
PD	Pharmacodynamic (when in reference to pharmacodynamic assessments)
PDK-1	Phosphoinositide-Dependent Kinase-1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI3K	Phosphoinositide 3-kinase
PI3KCA	Phosphatidylinositol-4,5-bisphosphate 3-kinase Catalytic Subunit Alpha
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PK	Pharmacokinetic
PO	Per Os (orally)
P-gp	P-glycoprotein
PR	Partial Response or Progesterone Receptor (depending on context)
PRO	Patient Reported Outcome
PS	Performance Status
PT	Prothrombin Time
PTEN	Phosphatase and Tensin Homolog
QD	Quaque Die (once daily)
QOL	Quality of Life

QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QT_c	QT Interval Corrected for Rate
QW	Quaque (once weekly)
RP2D	Recommended Phase 2 Dose
RECIST	Response Evaluation Criteria in Solid Tumors
CCI [redacted]	[redacted]
RPPA	Reverse Phase Protein Array
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease or Standard Deviation (depending on context)
SGOT	Serum Glutamic-Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic-Pyruvic Transaminase (ALT)
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SRSD	Single Reference Study Document
TCC	Transitional Cell Cancer
TKI	Tyrosine Kinase Inhibitor
Tmax	The Time of the Maximum Observed Concentration
t1/2	Half Life
TNBC	Triple Negative Breast Cancer
TORC1	TOR Complex 1
TORC2	TOR Complex 2
TTD	Time To Deterioration
UGT1A9	UDP-glucuronosyltransferase 1-9
UK	United Kingdom
ULN	Upper Limit of Normal
UPM	Unit Probability Mass
USPI	United States Package Insert
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential
WNL	Within Normal Limits

Appendix 2. 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 patiented 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.

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.

Appendix 2 Table 1. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	NewLesions	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:

Appendix 2 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 3. 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 4. Eastern Cooperative Oncology Group 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 5. Guidelines for Management of Hyperglycemia with PF-05212384

In clinical trials, PF-05212384 has been shown to have metabolic effects including hyperglycemia. The following guidelines are provided in an attempt to briefly inform Investigators as to the potential evaluation and treatments to be considered, and to attempt to standardize approaches to therapy. **These guidelines are not meant to replace institutional practices.**

On-study hyperglycemia management

- Patients with HbA1c ≥5.7%- home monitoring at least QD.
- Fasting blood glucose (FBG) assessed at every visit.
    - Repeat FBG in 1 week if ≥200 mg/dL.

Fasting Blood Glucose	Management[¥]

≥160 mg/dL on 2 readings 1 week apart	• For patients without history of DM
	  • Lifestyle modification.
	  • Initiate metformin therapy.*
	  • If FBG ≥200 mg/dL initiate home monitoring QD.
	  • If FBG >200-250 mg/dLafter 2 weeks of metformin:
	  • Continue metformin and add sulfonylurea.[¥] **
	• If FBG ≥250 mg/dL after 1 week
	  • Add sulfonylurea.**
	  or
	  • Add insulin and titrate to maintain FBG <200 mg/dL.
	Targets of treatment
	– Fasting/AC glucose: <160 mg/dL
	– Random glucose: <200 mg/dL
	– Avoid hypoglycemia
	• For patients with history of DM.
	  • Titrate current medications to maintain FBG <200 mg/dL.
	  • Consult with endorcrinologist/primary care physician who is following DM.

Symptomatic[§] Grade 3 (250-500 mg/dL)	• IV fluids and consider hospitalization. • Consider holding study drug dose until ≤ Grade 2 or baseline and then restarting at original dose level.
Grade 4	• IV fluids and consider hospitalization. • Consider holding study drug dose until ≤ Grade 2 or baseline and then restarting at 1 lower dose level.
Grade 4 despite optimal antihyperglycemic therapy	• IV fluids and consider hospitalization. • Discontinue treatment.
* Contraindicated in patients with renal insufficiency. [¥] Discontinue oral anti-hyperglycemics and monitor for hypoglycemia when study drug is interrupted for lengthy periods or is discontinued. ** Short acting agents (eg, repaglinide). [§] Symptoms such as, but not limited to hypotension, severe dehydration, severe metabolic abnormalities manifested as ECG changes.	

Appendix 6. Skin Toxicity Management with PF-05212384

In clinical studies, PF-05212384 has been shown to induce skin toxicities including rash and pruritis. The following guidelines are provided in an attempt to briefly inform Investigators as to the potential evaluation and treatments to be considered, and to attempt to standardize approaches to therapy. **These guidelines are not meant to replace institutional practices.**

The following charts may be used as a guide in determining %BSA when assessing the severity of rash. [source: O'Sullivan, Susan B., Schmitz, Thomas J. Physical Rehabilitation. 5th ed. F.A. Davis Company, Philadelphia, 2007. p. 1098, Fig 27.9]

Adult	
Anatomic structure	**Surface area**
Anterior head	4.5%
Posterior head	4.5%
Anterior torso	18%
Posterior torso	18%
Anterior leg, each	9%
Posterior leg, each	9%
Anterior arm, each	4.5%
Posterior arm, each	4.5%
Genitalia/perineum	1%

Adult, obese >80 kg	
Anatomic structure	**Surface area**
Head and neck	2%
Anterior torso	25%
Posterior torso	25%
Leg, each	20%
Arm, each	5%
Genitalia/perineum	0%

Appendix 6 Table 1. Management of Treatment Related Maculopapular Rash

Grade 1 (<10% of BSA)	Maintain study drug Start application of topical hydrocortisone to affected areas, eg: Alclometasone 0.05% cream to head and neck areas Mometasone 0.05% cream to body Weekly reassessment If worsening or lack of improvement after 2 weeks of treatment, add treatment for moderate maculopapular rash
Grade 2 (≥10% but ≤30% of BSA)	Maintain study drug Start application of topical hydrocortisone to affected areas, eg: Alclometasone 0.05% cream to the head and neck Mometasone 0.05% cream to body Start oral prednisone 0.5mg/kg QD Weekly reassessment If worsening or lack of improvement after 1 weeks of treatment, add treatment for severe maculopapular rash
Grade 3 (>30% BSA)	Study drug should be held until grade ≤1 Start application of topical treatments to affected areas: Alclometasone 0.05% cream to the head and neck Mometasone 0.05% cream to body Start oral prednisone 0.5mg/kg QD If skin rash worsens or does not improve with 2 weeks of topical or oral treatment, patient should be discontinued from study If rash is resolved to mild rash, resume study drug with 1 step dose reduction Oral corticosteroids should continue for at least one week after resumption of reduced dose of study drug. Discontinue patient from study treatment if severe or intolerable maculopapular rash recurs

Appendix 6 Table 2. Management of Treatment Related Pruritus

Grade 1	Maintain study drug Start topical treatment: Hypoallergenic moisturizing cream Antihistaminic creams Topical triamcinolone 0.1% cream Weekly reassessment If worsening or lack of improvement after 2 weeks of treatment, add treatment for moderate pruritus
Grade 2	Maintain study drug Start topical treatment: Hypoallergenic moisturizing cream Antihistaminic creams Topical triamcinolone 0.1% cream Start oral treatment: Antihistaminics or GABA antagonist (gabapentin or pregabalin) Weekly reassessment If worsening or lack of improvement after 2 weeks of treatment, add treatment for severe pruritus
Grade 3	Study drug should be held until grade ≤1 Start topical treatment: Hypoallergenic moisturizing cream Antihistaminic creams Topical triamcinolone 0.1% cream Start oral treatment: Antihistaminics or GABA antagonist (gabapentin or pregabalin) Start Doxepin 50mg BID Weekly reassessment If skin reactions do not improve with 2 weeks of symptomatic treatment, discontinue patient from study drug. Resume study drug at a reduced dose if recover to mild pruritus. Discontinue patient from study treatment if intolerable moderate or severe reaction recurs at a reduced dose.

Appendix 6 Table 3. Management of Treatment Related Dry Skin

Grade 1	Maintain study drug Start hypoallergenic moisturizing cream or ointment to the face BID and ammonium lactate 12% cream to the body BID Weekly reassessment If worsening or lack of improvement after 2 weeks of treatment, add treatment for moderate dry skin
Grade 2	Maintain study drugs Start hypoallergenic moisturizing cream or ointment to the face BID and ammonium lactate 12% cream to the body BID or salicylic acid 6% cream (if hyperkeratosic lesions are present) to the body BID Weekly reassessment If worsening or lack of improvement after 2 weeks of treatment, add treatment severe dry skin
Grade 3	Study drug should be held until recovers to mild dry skin Start hypoallergenic moisturizing cream or ointment to the face BID and ammonium lactate 12% cream to the body BID or salicylic acid 6% cream (if hyperkeratosic lesions are present) to the body BID Start triamcinolone 0.25% cream to eczematous areas bid. Reassess at least weekly If dry skin does not improve with 2 weeks of symptomatic treatment, discontinue patient from study. Resume study drugs at a reduced dose if dry skin recovers to mild dry skin. Discontinue patient from study treatment if intolerable moderate or severe dry skin recurs at a reduced dose.

Appendix 7. Dacomitinib Adverse Event Management Guidelines

In all instances, it is recommended that patients be instructed at time of starting drug therapy to call the Investigator/Site if no improvement in symptoms has been observed after 24 hours of patient taking the recommended/optimal pharmacologic treatment.

Abbreviations:

BSA: Body Surface Area

ADL: Activities of Daily Living.

- *Instrumental ADL* refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- *Self care ADL* refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden. (Definitions per CTCAEv4).

GABA: gamma-Aminobutyric Acid

DIARRHEA

- Patients should be encouraged to drink 8 to 10 large glasses of clear liquids per day while on study in order to maintain adequate hydration.

- General dietary measures to limit impact of diarrhea could include:

    - Stop all lactose-containing products in patients with evidence of lactose intolerance;

    - Eat frequent small meals if experiencing increased frequency of stools;

    - Consider low fat regimen enriched with bananas, rice, applesauce, and toast.

	Diarrhea Management Guideline
Grade of Event	Management / Next Dose
Grade 1: increase of <4 stools per day over baseline;	Loperamide 4 mg at the first onset of diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. (During the night the patient may take 4mg of loperamide every 4 hours.) Fluid intake of at least 2 liters (L) should be maintained to avoid dehydration: patients are to drink 8-10 large glasses of clear liquids. Consideration for maintenance of electrolyte balance would include electrolyte-containing drinks, broth, clear juices. ***Study Treatment***: should be continued at same dose.
Grade 2: increase of 4-6 stools per day over baseline;	Loperamide as above, or consider use of diphenoxylate hydrochloride and atropine sulfate formula (eg Lomotil®, Diarced®, Co-Phenotroope®) at standard doses Fluid intake of at least 2 L should be maintained to avoid dehydration. Monitor patient closely and consider intravenous hydration. ***Study Treatment:*** If not improved to ≤ Grade 1 within 24 hrs despite use of loperamide, hold treatment until Grade ≤1. If diarrhea of > Grade 1 recurs after initial improvement, consider reduction of 1 dose level.
Grade 3: increase of ≥7 stools per day over baseline; or incontinence; or limiting self care ADL: or hospitalization indicated	Oral therapy with diphenoxylate hydrochloride and atropine sulfate formula, or tincture of opium. Fluid intake of at least 2 L should be maintained, intravenously if necessary. Consider use of octreotide (Sandostatin®) 100-150 microgram (μg) subcutaneously twice daily with escalation to 500 μg three times daily. Consider hospitalization if does not improve to Grade 2 within 24 hours, or in presence of fever, abdominal pain,etc. ***Study Treatment:*** Hold therapy. Upon resolution to ≤ Grade 1, resume therapy with consideration of dose reduction
Grade 4: life-threatening	Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of Investigator for fever, leucocytosis, marked dehydration, etc. ***Study Treatment:*** Hold until ≤ Grade 1. Mandatory dose reduction when dosing resumed

DERMATOLOGIC TOXICITY

Acneiform/ Papulopustular Rash:

	Acneiform/ Papulopustular Rash Management Guideline
Grade 1: <10% body surface area (BSA) papules and/or pustules (with or without symptoms of pruritis or tenderness)	**Topical steroids *** **And** **Topical antibiotic bid** (clindamycin 1 - 2%, erythromycin 1% - 2%, metronidazole 1%)
Grade 2: 10 to 30% BSA papules and / or pustules (with or without symptoms of pruritis or tenderness), or psychosocial impact, or limited instrumental ADL	**Oral antibiotic for at least 4 weeks** (doxycycline 100 mg BD, minocycline 100mg bd or oxytetracycline 500 mg BD); Stop topical antibiotic if being used **And** **Topical steroids ***
Grade 3: >30% BSA papules and / or pustules (with or without symptoms of pruritis or tenderness); *or* • limiting self-care ADL: or • associated with local superinfection with oral antibiotics indicated	**Oral antibiotic for 4 weeks** (doxycycline 100 mg BD, minocycline 100mg bd or oxytetracycline 500 mg BD) **If infection suspected** (yellow crusts, purulent discharge, painful skin/nares): switch oral antibiotic to broad spectrum/gram negative cover for at least 10 days consider skin swab for bacterial culture, **And** **Topical steroids (continue)*** Consider dermatology consultation
*** Moderate/Low strength steroids such as:**	Triamcinolone acetonide 0.025% Desonide 0.05% Aclometasone 0.05% cream Fluticasone propionate 0.05% For patients intolerant or allergic to tetracycline antibiotics, use an antibiotic with Staphloccoccus coverage (eg, cephalexin, sulfamethoxazole/ trimethoprim)

Dry Skin/ Xerosis:

Prophylaxis against dry skin would include:

- Initiation of skin moisturizing cream or ointment regimen upon establishment of eligibility (ie prior to first dose). (avoid skin lotions, as they may contain alcohol).
- Avoidance of excessive exposure to hot water during showering/bathing.
- Avoidance of household tasks involving immersion in hot water/ detergent/ solvents.
- Avoidance of excessive sun exposure/tanning. Use sunscreen containing zinc oxide or titatinium dioxide with SPF at least 30: apply every two hours when exposed to sun.

	Xerosis/ Dry Skin Management Guideline
Grade 1: <10% BSA and no associated erythema or pruritis	Over-the-counter Moisturizing cream or ointment to face bid **AND** Ammonium lactate 12% (or equivalent) cream to body bid
Grade 2: 10 to 30% BSA and associated with erythema or pruritis; or limited instrumental ADL	OTC Moisturizing cream or ointment to face bid; **AND** Ammonium lactate 12% cream OR salicylic acid 6% cream to body bid
Grade 3 >30% BSA and associated with pruritis; or limiting self care ADL	OTC Moisturizing cream or ointment to face bid; **AND** Ammonium lactate 12% cream OR salicylic acid 6% cream to body bid **AND** Topical steroid* to eczematous areas bid
*Moderate/Low strength steroid such as:	*Triamcinolone acetonide 0.025% (Aristocort A cream)* Desonide 0.05% (DesOwen cream, lotion) Aclometasone 0.05% cream (Allocate cream) Fluticasone propionate 0.05%

Paronychia:

	Paronychia Management Guideline
Grade 1 Nail fold edema or erythema; or disruption of the cuticle	Topical Antibiotics and vinegar soaks *
Grade 2 Localized intervention indicated; or oral intervention indicated (eg, antibiotic, antifungal, antiviral); or nail fold edema or erythema with pain; or associated with discharge or nail plate separation; or limiting instrumental ADL	Topical antibiotics and vinegar soaks* Apply silver nitrate weekly
Grade 3 Surgical intervention, or IV antibiotics indicated; or limiting self care ADL	Topical antibiotics and vinegar soaks* Apply silver nitrate weekly Surgical consultation as needed
*Topical antibiotics/ vinegar soaks	*Topical antibiotics: Clindamycin 1%, erythromycin 1%* *Vinegar soaks consist of soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day* ± For a video on how to apply silver nitrate, visit: http://www.youtube.com/watch?v=HF5oopqheJY

Pruritis/Itching:

Prophylaxis against dry skin would include:

- Initiation of skin moisturizing regimen prior to first dose. Non-scented emollient skin cream should be used;
- Avoidance of excessive exposure to hot water during showering/bathing;
- Avoidance of household tasks involving immersion in hot water/ detergent/ solvents;
- Avoidance of excessive sun exposure/ tanning. Use sunscreen containing zinc oxide or titatinium dioxide with SPF at least 30: apply every two hours when sun exposure is anticipated.

	Pruritis Management Guideline
Grade 1: Mild or localized; or topical intervention indicated	Topical steroid moderate strength (eg, Triamcinolone acetonide 0.025% Desonide 0.05% Aclometasone 0.05% cream Fluticasone propionate 0.05% or Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
Grade 2 Intense or widespread, intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); or oral intervention indicated; or limiting instrumental ADL	Topical steroid moderate strength or Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily **AND** Oral antihistamines
Grade 3: Intense or widespread, constant; or limiting self care ADL or sleep; or oral corticosteroid or immunosuppressive therapy indicated	Oral antihistamines **AND** GABA agonists (gabapentin or pregabalin) or Doxepin
	Antihistamines: diphenhydramine 25-50 mg TID; hydroxizine 25mg TID; fexofenadine 60mg TID GABA agonists (adjust if renal impairment): Gabapentin 300 mg every 8 hours or Pregabalin 50-75 mg every 8 hours Tricyclics: Doxepin 25-50 mg every 8 hours

MUCOSITIS

Patients who have not had a dental check up within 6 months prior to start of dosing are encouraged to do so, especially to identify any persistent issue related to recent chemotherapy. Once on treatment, patients are to consult the site health care team prior to

undertaking any dental or oral surgery procedure to determine if it would be appropriate to proceed depending on presence of any ongoing mucosal inflammation/ stomatitis.

Between scheduled visits, patient self-report of oral mucosal discomfort or of visible changes in appearance to oral mucosa is encouraged. Periodic systematic examination of the oral cavity is required at scheduled visits and as otherwise indicated by patient self-report between visits.

Patients should practice good oral care including a soft-bristle toothbrush replaced frequently and use of bland rinses or moisturizers.

Regular use of warm water non-medicated saline rinse is recommended if stomatitis develops. Frequent sips of water during meals may assist swallowing and therefore maintain caloric intake and hydration in patients experiencing oral pain

Use of chlorhexidine is to be avoided.

Topical anesthetics or systemic analgesics may be used as indicated in judgment of the Investigator and according to local clinical practices. Topical steroid rinses have been reported to be helpful in severe cases (eg dexamethasone 0.5 mg/5 ml swish and expectorate four times daily).

Consultation with nutritionist is to be considered if toxicity may compromise maintenance of adequate caloric intake.

Keratoconjunctivitis

	Keratoconjunctivtis Guideline
Grade 1 Asymptomatic or mild symptoms; intervention not indicated	No intervention or dose modification is mandated
Grade 2: Symptomatic; topical intervention indicated; or limiting instrumental ADL	Preservative free artificial tears, ointments, and /or other therapies as clinically indicated, with a follow-up examination within 2 weeks to include slit-lamp and fundoscopic exam as per the Investigator judgment. ***Study Treatment***: If symptom lasts ≥2 weeks, withhold treatment until≤ Grade 1 and then reduce one dose level.
Grade 3: Limiting self care ADL	Preservative free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks to include slit-lamp and fundoscopic exam as per the Investigator judgment. ***Study Treatment:*** Drug should be withheld until recovers to≤ Grade 1 and then reduce one dose level.

PULMONARY TOXICITY

In the event of new onset of dyspnea, persistent cough, or other pulmonary symptoms, treatment with either drug should be stopped until patient can be adequately evaluated for possible development of drug related interstitial lung disease; dose modification is not appropriate in this setting. Patients should be counseled throughout treatment to alert investigator or designated team member immediately if they develop new or worsening respiratory symptoms. If following discussion between the sponsor and the investigator it is concluded that a thorough investigation has excluded treatment-induced pulmonary toxicity, and less than 2 weeks have elapsed off treatment, treatment may resume.

Appendix 8. CYP2D6 Substrates

For CYP2D6 substrates, prohibited drugs and drugs for which substitution, dose modification and/or monitoring is advised are listed below. This listing is not an all inclusive list, and will be monitored by Sponsor study team for required updates (addition, deletion) but in all instances Investigators should review potential for drug-drug interaction for concomitant medications and take appropriate measures of substitution or dose modification.

CODE	DRUG	THERAPEUTIC CLASS	CODE	DRUG	THERAPEUTIC CLASS
S	**amiflamine**	Monoamine Oxidase Inhibitors (MAOIs)	HS	**metoprolol**	Alpha/Beta Adrenergic Antagonists
HS	**amitriptyline**	Tricyclics and Tetracyclics	S	**mexiletine**	Antiarrhythmics
S	**aripiprazole**	Antipsychotics	S	**mianserin**	Tricyclics and Tetracyclics
HS	**atomoxetine**	Psychostimulants	S	**mirtazapine**	Tricyclics and Tetracyclics
S	**brofaromine**	Monoamine Oxidase Inhibitors (MAOIs)	HS	**nebivolol**	Alpha/Beta Adrenergic Antagonists
S	**bufuralol**	Alpha/Beta Adrenergic Antagonists	S	**nefazodone**	Serotonin Modulators
S	**carvedilol**	Alpha/Beta Adrenergic Antagonists	S	**nicergoline**	Vasodilators
S	**chlorpheniramine**	H-1 Receptor Antagonists	S	**nortriptyline**	Tricyclics and Tetracyclics
S	**chlorpromazine**	Antipsychotics	S	**(S)-ondansetron**	Serotonin HT3 Receptor Antagonists
S	**citalopram**	Serotonin Reuptake Inhibitors (SSRIs)	S	**oxycodone**	Opioids
S	**clomipramine**	Tricyclics and Tetracyclics	S	**pactimibe**	Other Antilipemics
S	**clozapine**	Antipsychotics	S	**paroxetine**	Serotonin Reuptake Inhibitors (SSRIs)
PD	**codeine**	Opioids	S	**perhexiline**	Vasodilators
S	**debrisoquine**	Other Antihypertensives	HS	**perphenazine**	Antipsychotics
HS	**desipramine**	Tricyclics and Tetracyclics	S	**phenformin**	Biguanides
S	**dexfenfluramine**	Anorexics	P	**pimozide**	Antipsychotics
HS	**dextromethorphan**	Antitussives	HS	**prajmaline**	Antiarrhythmics
S	**dihydrocodeine**	Opioids	P	**procainamide**	Antiarrhythmics
S	**donepezil**	Anticholinesterase Inhibitors	S	**propafenone**	Antiarrhythmics
HS	**doxepin**	Tricyclics and Tetracyclics	S	**propranolol**	Alpha/Beta Adrenergic Antagonists
S	**duloxetine**	Ser-Nor Reuptake Inhibitors (SNRIs)	S	**ranolazine**	Cardiovascular Drugs
S	**encainide**	Antiarrhythmics	S	**repinotan**	Serotonin Receptor Agonist
S	**fesoterodine**	Muscarinic Antagonists	S	**risperidone**	Antipsychotics
S	**flecainide**	Antiarrhythmics	S	**ritonavir**	Protease Inhibitors
S	**fluoxetine**	Serotonin Reuptake Inhibitors (SSRIs)	S	**sabeluzole**	CNS Agents
S	**fluphenazine**	Antipsychotics	S	**sparteine**	Antiarrhythmics
HS	**fluvoxamine**	Serotonin Reuptake Inhibitors (SSRIs)	PD	**tamoxifen**	Antineoplastic Hormonal
S	**gefitinib**	Kinase Inhibitors	S	**tamsulosin**	Alpha/Beta Adrenergic Antagonists
S	**haloperidol**	Antipsychotics	HS	**tetrabenazine**	CNS Agents
PD	**hydrocodone**	Opioids	P	**thioridazine**	Antipsychotics
S	**iloperidone**	Antipsychotics	S	**timolol**	Alpha/Beta Adrenergic Antagonists
S	**imipramine**	Tricyclics and Tetracyclics	HS	**tolterodine**	Muscarinic Antagonists
S	**lasofoxifene**	Estrogen Receptor Modulators	PD	**tramadol**	Other Analgesics
PD	**loratadine**	H-1 Receptor Antagonists	HS	**traxoprodil**	Neuroprotectors
S	**maprotiline**	Tricyclics and Tetracyclics	S	**trazodone**	Serotonin Modulators
S	**methadone**	Opioids	S	**trimipramine**	Tricyclics and Tetracyclics
S	**methamphetamine (MA)**	Recreational Drugs	HS	**tropisetron**	Serotonin HT3 Receptor Antagonists
S	**3,4-methylenedioxy-MA**	Recreational Drugs	S	**venlafaxine**	Ser-Nor Reuptake Inhibitors (SNRIs)
HS	**methoxyphenamine**	Beta Adrenoreceptor Agonist	HS	**vernakalant**	Antiarrhythmics
S	**Methylphenidate**	Psychostimulants	S	**zuclopenthixol**	Antipsychotics
S	**Metoclopramide**	Other Antiemetics			
HS	High likelihood of supratherapeutic exposure in combination with dacomitinib; dose-reduction and clinical monitoring IS required, if co-administration cannot be avoided: starting dose when coadministration with dacomitinib: 25% of original dose		P	Narrow therapeutic Index : Prohibited in combination with dacomitinib	
PD	pro-drug: active ingredient ONLY or partially upon CYP2D6 metabolism. High likelihood of subtherapeutic exposure in combination with dacomitinib		S	High likelihood of supratherapeutic exposure in combination with dacomitinib; clinical monitoring is required and dose-reduction may be necessary	
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Appendix 9. Management of Allergic Reactions or Anaphylaxis

In the event of allergic, infusion or hypersensitivity reactions, investigators should institute treatment measures according to best medical and nursing practice.

The following treatment guidelines should be employed:

If chills and fever occur, the infusion should be interrupted. Patients may be treated symptomatically and the infusion should be restarted at 50% of the original rate.

NCI-CTCAE Grade 1 allergic, infusion or hypersensitivity reaction

1. Decrease PF-05212384 infusion rate by 50% and monitor for worsening condition. If the reaction worsens, stop the infusion. Protocol treatment will be discontinued.

NCI-CTCAE Grade 2 allergic, infustion or hypersensitivity reaction

1. Stop PF-05212384 infusion.

2. Administer bronchodilators, oxygen, acetaminophen, etc. as medically indicated.

3. Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop infusion. Protocol treatment will be discontinued.

NCI-CTCAE Grade 3 or Grade 4 allergic, infusion or hypersensitivity reaction or anaphylaxis

1. A Grade 3 hypersensitivity reaction consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or asymptomatic hypotension not requiring treatment.

2. A Grade 4 hypersensitivity reaction (ie, anaphylaxis) is a life-threatening event characterized by the same symptoms as in a Grade 3 reaction but also complicated by symptomatic hypotension or oxygen saturation of 70% or less.

Treatment of Grade 3 or Grade 4 allergic, infustion or hypersensitivity reaction or anaphylaxis

1. Stop the PF-05212384 infusion immediately and disconnect infusion tubing from the patient.

2. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically indicated.

3. Telephone Sponsor or designated representative to report an SAE and fax SAE worksheet.

For a NCI-CTCAE Grade 3 or 4 hypersensitivity reaction, protocol treatment will be discontinued.

Re-treatment following Grade 1 or Grade 2 allergic, infustion or hypersensitivity reaction

1. Once the PF-05212384 infusion rate has been decreased due to a reaction, it will remain decreased for all subsequent infusions.

2. If the patient has a second reaction at the lower infusion rate, the infusion should be stopped and the patient should receive no further PF-05212384.

3. If the patient experiences a Grade 3 or 4 allergic reactionor anaphylaxis at any time, the patient should receive no further PF-05212384.

4. If there are questions concerning whether an observed reaction is consistent with an allergic reaction or anaphylaxis, the medical monitor should be contacted immediately to assist with grading the reaction.

PK and PD sampling should continue as long as the sampling does not interfere with the medical treatment of the patient.

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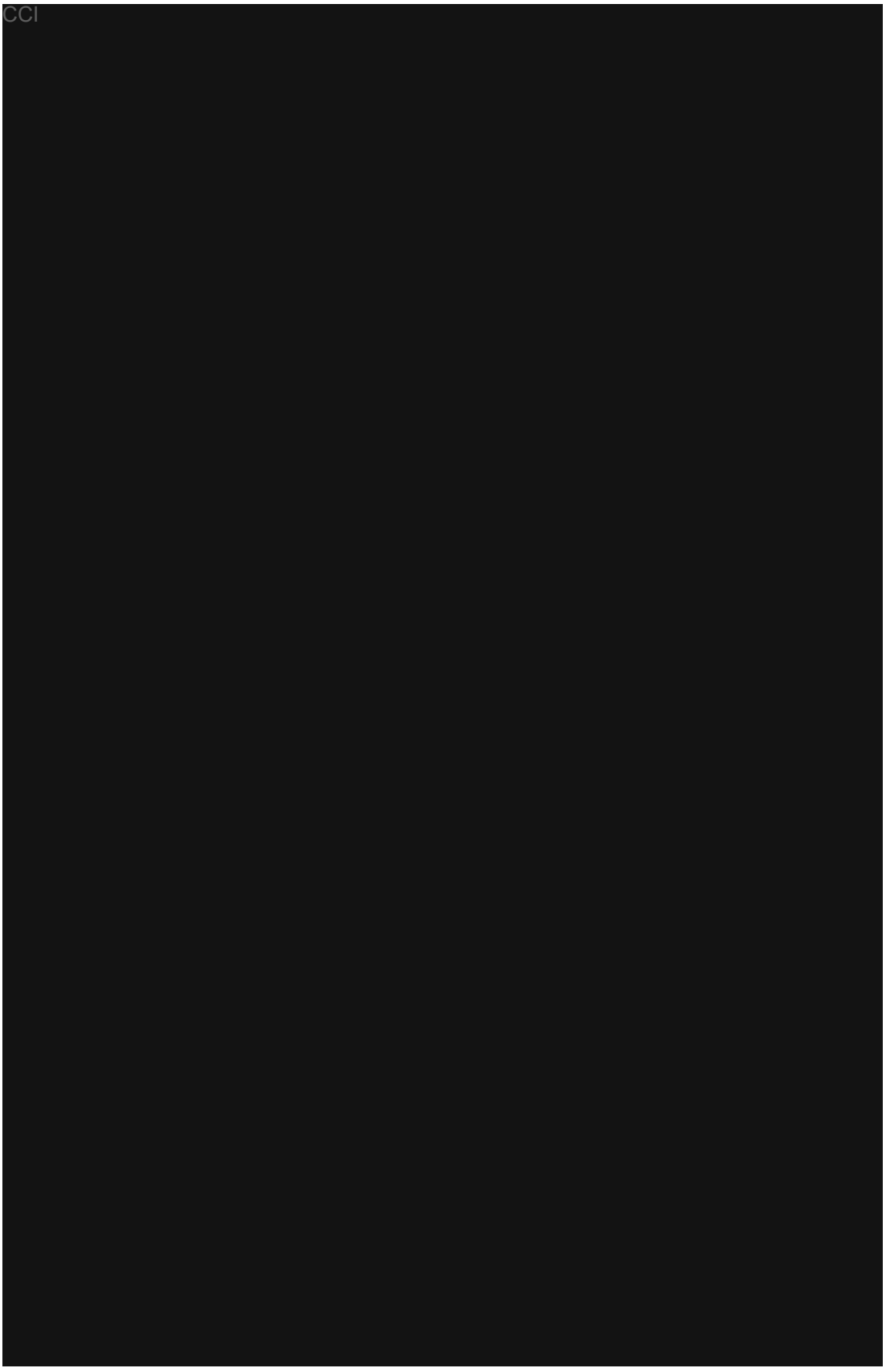

ENGLISH

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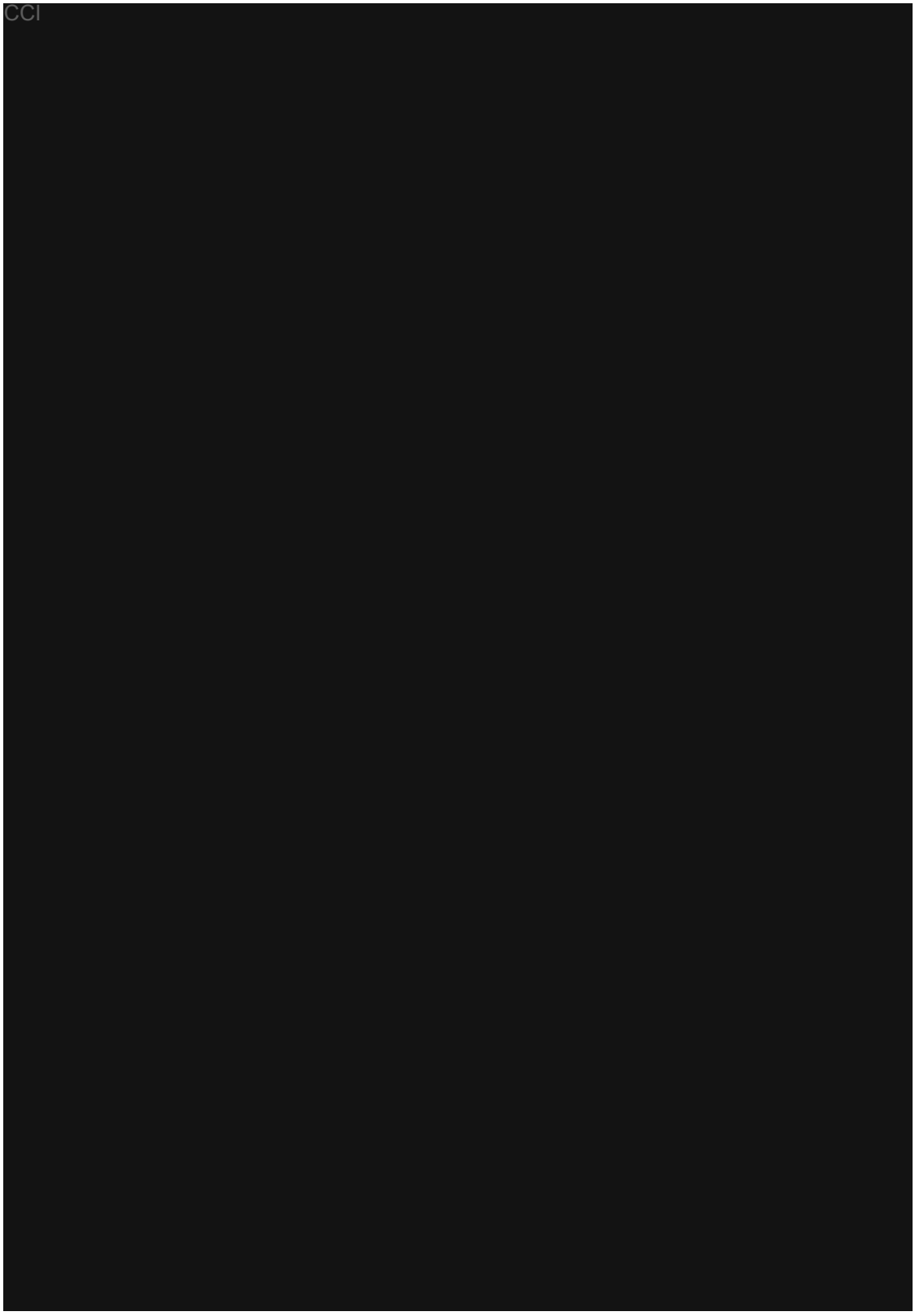

Appendix 11. BR23 English

ENGLISH

EORTC QLQ - BR23

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.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	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
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4