Protocol B2151002

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

Statistical Analysis Plan

(SAP)

Version: **5**

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment 1 (SAP version 2) was for updates based on protocol amendments through amendment 3. The dose levels for PF-05212384 were increased.

Amendment 2 (SAP version 3) is for Protocol Amendment 5. Two expansion arms are added to Arm B in TNBC patient. The SAP amendment also makes updates to be consistent with the protocol.

In addition, for SAP version 3, all biomarker and pharmacodynamics analyses have been removed from this SAP and will be contained in a separate supplemental SAP.

SAP version 4 updates the PFS definition to take into account an extended time between tumor assessments after a patient was on study for 13 cycles, per the protocol.

SAP version 5 re-incorporates the biomarker and pharmacodynamics analyses into the SAP.

2. INTRODUCTION

2.1. Study Design

2.1.1. Overall 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.

The three arms will be designated Arms A, B and C.

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.[1,2] 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 dose limiting toxicities (DLTs).

In Arm C, 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.[3]

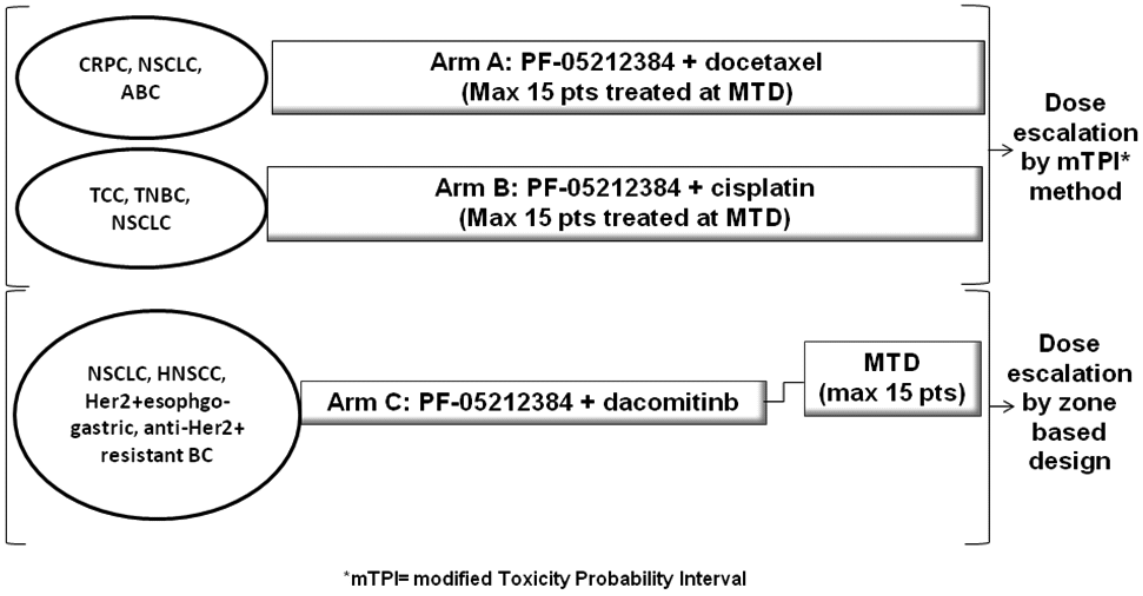
In all arms, dose escalation will proceed until a maximum tolerated dose (MTD) or MTDs are declared, or the Maximum Allowable Dose (the highest planned dose) is reached.

For Arm A and B it is expected that 10-15 patients will be treated at the MTD during dose finding. In Arm C, a minimum of 10 and maximum of 15 patients will be treated at the MTD to further confirm safety and tolerability and to explore early signs of efficacy. Per Protocol Amendment 5, there will be an expansion cohort in Arm B for TNBC patients. It is planned that 30 response evaluable patients will be enrolled, 15 patients into each of the 2 arms (1st line and 2nd/3rd line).

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.

The overall study design is show in Figure 1.

Figure 1. Overall Dose Escalation 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; HNSCC: Head and neck squamous cell cancer; BC: Breast cancer.

In the dose escalation, to understand the single-dose safety and single dose pharmacokinetics (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.

The expansion arms do not have a lead-in dose, PK assessments will begin on Cycle 1 Day 1.

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, continuation within the study will be discussed with the Sponsor.

2.1.2. Dose Levels to Be Tested (Dose Escalation)

The possible dose levels for Arms A, B, and C dose escalation are shown in Table 1. 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.

Table 1. 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.

Arm B		
Dose Level	***PF-05212384 mg/wk IV***	**Cisplatin mg/m^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 will not be explored since dose level exceeds MTD*

2.1.3. Criteria for Dose Assignment

2.1.3.1. Criteria for Dose Assignment for Arms A and B

In Arms A and B, the dose assignment recommendations of the method are provided in Figure 2. Patients will be enrolled in cohorts of 3 patients, with the flexibility of other cohort sizes. The starting dose levels will be A1 and B1 for Arms A and B, respectively. For any subsequent cohort of patients, the recommended dose assignment action will be based on the total number of patients with DLTs among all patients treated at the current dose level. For example, if a cohort of 3 patients are treated at dose level A1 for the first time and one of the patients experience a DLT, then it is recommended that the next cohort of patients 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 no additional DLTs are 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).

Details of the interval design to be used for Arms A and B in this study are provided in Appendix 2.1.

The actual dose level selected for the next cohort of patients will take into account the recommended dose level 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.*

For Arms A and B, if the DLT rates are not monotonically increasing the MTD will be estimated based on isotonic regression of DLT rates of all dose levels at the end of the study. The MTD will be the dose that has a DLT rate that is less than or equal to 32%. 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.

Figure 2. Recommended Action Based on Cumulative Dose Limiting Toxicities at Current Dose Level (Arms A and B)

		Cumulative number of patients treated at the current dose level													
		2	3	4	5	6	7	8	9	10	11	12	13	14	15
Cumulative number of patients with DLTs at the current dose level	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
Target DLT rate = 25%

2.1.3.2. Criteria for Dose Assignment for Arm C

The starting dose level will be C1. Dose escalation will proceed according to the sequence in Table 2 until an MTD (or two MTDs) is declared.

Table 2. 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.

*C2h and C3h from the original protocol will not be pursued due to observing 2 DLTs in dose level C1h.

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 (see Table 2). To open enrollment to dose level C2h, the DLT data from the preceding two lower dose levels C2 and C1h must both indicate dose escalation, ie, no DLTs were 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 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 none 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 in an expansion cohort. Up to a maximum of 15 patients will be treated in the expansion cohort to better define the tolerability and to evaluate clinical activity.

It is expected that up to 50 patients will be enrolled into Arm C, including the MTD expansion cohort.

2.1.4. Safety and Efficacy Expansion in TNBC Arm B

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 at the 180mg PF-05212384 dose in combination with cisplatin at 75 mg/m^2. There will be two arms: Arm 1 for 1st line TNBC patients and Arm 2 for 2nd/3rd line TNBC patients.

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.

Up to 15 response evaluable patients (see Section 5.4.1) per arm will be treated in the expansion.

2.1.5. DLT Definition (All Arms)

Refer to the protocol for the definition of DLT in this study.

2.2. Study Objectives

2.2.1. Primary Objectives

2.2.1.1. Original Protocol through Amendment 4

- 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.

2.2.1.2. Amendment 5 (Expansion only)

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

2.2.2. Secondary Objectives

2.2.2.1. Original Protocol through Amendment 4

- 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.

2.2.2.2. Amendment 5 (Expansion only)

- 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.

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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

3.1. Unblinding

This is an open label study, thus unblinding is not applicable.

3.2. Interim Analysis

There is no official interim analysis.

3.3. Final Analysis

The final analysis will be performed at the time of official database release for clinical study report unless if there are ongoing patients in which case a final CSR will be written with a supplemental CSR to follow.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There are no formal statistical hypotheses.

4.2. Statistical Decision Rules

There are no formal statistical decision rules.

5. ANALYSIS SETS

5.1. Full Analysis Set

The full analysis set includes all enrolled patients.

5.2. Per Protocol Analysis Set (DLT Evaluable Set)

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 study drug in the combination (provided that the reduction is not due to toxicity attributable to the combination).

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

5.3. Safety Analysis Set

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

5.4. Other Analysis Sets

5.4.1. Response Analysis Set

The response analysis set consists of all patients who receive at least one dose of study medication, have the disease under study, and who have an adequate baseline tumor assessment (see Appendix 1 for details).

5.4.2. Pharmacokinetic Concentration Analysis Set

The PK concentration analysis set is defined as all enrolled patients who start treatment and who have concentration measurement recorded for at least one time point.

5.4.3. Pharmacokinetic Parameter Analysis Set

The PK parameter analysis set is defined as all enrolled patients who start treatment and 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.

5.4.4. Molecular Profiling Tumor Analysis Set

The molecular profiling tumor analysis set is defined as all enrolled patients who start treatment and have baseline archived tumor biopsy formalin fixed paraffin embedded (FFPE) sample (or fresh FFPE if archived is not available) successfully analyzed for at least one of the selected biomarkers.

5.4.5. Expression Tumor Analysis Set

The 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.

Selected biomarkers include those related to pathway inhibition (pharmacodynamics) and resistance signaling.

5.4.6. Serum Pharmacodynamic Analysis Set

The 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.

PD biomarkers include serum glucose, insulin, and HbA1c from safety laboratory tests.

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5.4.9. QTc Analysis Set

The QTc analysis set is defined as all enrolled patients who have at least one ECG assessment after receiving study drug or study drugs. Analyses of changes from baseline also require a baseline ECG assessment.

For the purpose of QTc versus concentration analysis, the analysis set is defined as all enrolled patients who have at least one of the planned time matched PK concentration and ECG assessments.

5.4.10. PRO Analysis Set

The PRO analysis set is defined as all enrolled patients who started treatment on study drug and who completed a baseline assessment and at least one post-baseline assessment.

The PRO analysis set will be the primary dataset to determine change from baseline scores and the proportion of patients with scores that improved, worsened, or remained stable over treatment.

5.5. Treatment Misallocations

Patients will be analyzed based on the arm to which they are initially assigned unless the following occurs:

- **Assigned but not treated:** they will not be included in safety or efficacy analyses.
- **Assigned but received/took incorrect treatment (ie, wrong arm or wrong dose level):** they will be reported under the treatment they actually received for safety and efficacy analyses (ie, as treated).

5.6. Protocol Deviations

The following describes any protocol deviations that relate to the statistical analyses or analysis sets.

5.6.1. Deviations Occurring Prior to Treatment Start

Pre-treatment deviation affecting the response analysis set: patients who are found to have inadequate baseline assessment. Refer to Section 5.4.1 for handling of these deviations.

5.6.2. Deviations Occurring Post-Treatment Start

Major post-treatment start deviation affecting the safety analysis set: patients received incorrect treatment. Refer to Section 5.5 for handling of these deviations.

Major post-treatment start deviations affecting the per protocol analysis set include: 1) patients received less than 75% of the planned Cycle 1 dose of either study drug in the combination (provided that the reduction is not due to toxicity attributable to the combination), and 2) patients received more than 125% of the planned Cycle 1 dose of either study drug in the combination. Refer to Section 5.2 for handling of these deviations.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

Efficacy endpoints are defined differently for patients without measurable disease at baseline compared to those with measurable disease at baseline. Efficacy is a primary endpoint for the Arm B expansion arms and secondary endpoint for the dose escalation arms. Patients in the expansion arms are required to have measureable disease and to have responses confirmed.

6.1.1. Efficacy Endpoints for Patients WITH Measurable Disease in the Dose Escalation

Objective response status at each evaluation [complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or indeterminate] will be assessed by the Investigator according to the RECIST v1.1 guidelines.

Best overall response is defined as the best response recorded from first dose of study treatment until disease progression. It is derived from the sequence of objective statuses. Objective statuses after the first PD or the start of a new anticancer treatment are excluded from consideration. Categories include CR, PR, SD, PD and indeterminate (not evaluable).

- CR: At least one objective status of CR documented before progression;
- PR: At least one objective status of PR documented before progression, but not qualifying as CR;
- SD: At least one objective status of SD documented at least 6 weeks after first dose of study treatment and before progression, but not qualifying as CR, or PR. (note: 6 weeks is chosen based on the first post-baseline tumor assessment scheduled at 6 weeks from C1D1, adding at least 1 week between lead-in dose and C1D1, and allowing 5 days early for the first post-baseline tumor assessment);
- PD: Objective status of progression within 15 weeks of first dose of study treatment, not qualifying as CR, PR, or SD. (note: 15 weeks is chosen based on the second post-baseline tumor assessment scheduled at 12 weeks from C1D1, adding up to 2 weeks between lead-in dose and C1D1, and allowing 5 days delay for the second post-baseline tumor assessment);
- Indeterminate: Progression not documented within 15 weeks of first dose of study treatment and no other response category applies.

Objective response is defined as CR or PR.

Clinical benefit response is defined as CR or PR at any time, or non-CR/non-PD or SD for at least 24 weeks from first dose of study treatment.

For tumor measurements, in the event that a lesion is "too small to measure" a measurement of 5 mm will be used for calculations to assess best overall response.

6.1.2. Efficacy Endpoints for Patients WITHOUT Measurable Disease in the Dose Escalation

Objective response status at each evaluation (CR, PD, non-CR/non-PD, or indeterminate) will be assessed by the Investigator according to the RECIST v1.1 guidelines.

Best overall response is defined as the best response recorded from first dose of study treatment until disease progression. It is derived from the sequence of objective statuses. Objective statuses after the first PD or the start of a new anticancer treatment are excluded from consideration. Best overall responses will include the following categories: CR, non-CR/non-PD, PD, and Indeterminate.

- CR: At least one objective status of CR documented before progression.
- Non-CR/non-PD: At least one objective status of non-CR/non-PD documented at least 6 weeks after first dose of study treatment and before progression, but not qualifying as CR.
- PD: Objective status of progression within 15 weeks of first dose of study treatment, not qualifying as CR, or non-CR/non-PD.
- Indeterminate: Progression not documented within 15 weeks of first dose of study treatment and no other response category applies.

6.1.3. Efficacy Endpoints for Patients in the Arm B Expansion Arms

Objective response status at each evaluation [complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or indeterminate] will be assessed by the Investigator according to the RECIST v1.1 guidelines.

Best overall response is defined as the best response recorded from first dose of study treatment until disease progression. It is derived from the sequence of objective statuses. Objective statuses after the first PD or the start of a new anticancer treatment are excluded from consideration. Categories include CR, PR, SD, PD and indeterminate (inevaluable).

- **CR**: Two objective statuses of CR a minimum of four weeks apart documented before progression and start of new anti-cancer therapy.
- **PR**: Two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of four weeks apart documented before progression and start of new anti-cancer therapy, but not qualifying as CR. Sequences of PR- Stable- PR are considered PRs as long as the two PR responses are observed at a minimum of 4 weeks apart.

- **SD**: At least one objective status of SD documented at least 6 weeks after first dose of study treatment and before progression and the start of new anti-cancer therapy, but not qualifying as CR, or PR. An assessment window of -5 days is allowed per the protocol to still qualify as SD.

- **PD:** Objective status of progression within 13 weeks of first dose of study treatment, not qualifying as CR, PR, or SD (note that 13 weeks is chosen based on 2 tumor assessments and to allow for ~5 days delay for the second post-baseline tumor assessment per the protocol).

- **Indeterminate**: Progression not documented within 13 weeks of first dose of study treatment and no other response category applies.

Objective response is defined as CR or PR.

Clinical benefit response is defined as CRor PR at any time, or non-CR/non-PD or SD for at least 24 weeks from first dose of study treatment.

Progression-free survival (PFS) is defined as the time from first dose of study treatment to date of first documentation of progression or death due to any cause, whichever occurs first. Documentation of progression must be by objective disease assessment as defined by RECIST v1.1.

Patients last known 1) to be alive, 2) not to have started new anti-cancer treatment, and 3) to be progression-free, and who have a baseline and at least one on-study disease assessment, will be censored at the date of the last objective disease assessment that verified lack of disease progression.

Patients with inadequate baseline disease assessment will be censored at the date of first dose of study treatment.

Patients with no on-study disease assessments will be censored at the date of first dose of study treatment unless death occurred prior to 13 weeks since first dose (in which case the death is an event).

Patients starting new anti-cancer treatment prior to progression will be censored at the date of last objective disease assessment documenting no progression prior to the new treatment.

Patients with documentation of progression or death after an unacceptably long interval (>13 weeks within the first 12 cycles or > 19 weeks from cycle 13 on) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

Censoring and Event details are listed in Appendix 2.2.

For tumor measurements, in the event that a lesion is “too small to measure” a measurement of 5 mm will be used for calculations to assess best overall response.

6.2. Safety Endpoints

6.2.1. Treatment Emergent Adverse Events

Adverse Events (AEs) will be graded by the Investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Causal relationship of an AE to study treatment will be assessed by the investigator. As there are two study drugs, an AE may be attributed to either or both of the study drugs.

An adverse event is a **treatment-emergent adverse event (TEAE) if**:

- The event occurs for the first time after the start of study treatment and within 28 days after final dose of study treatment and was not seen prior to the start of treatment, or;
- The event was seen prior to the start of study treatment but increased in CTCAE grade after the start of study treatment and within 28 days after final dose of study treatment.

6.2.2. Dose Limiting Toxicity – Primary Endpoint

A **DLT** is any of the TEAEs meeting the DLT criteria as specified in the protocol that occurs in the first cycle of treatment (starting from the lead-in dose through Cycle 2 Day 1 for this purpose) which are possibly attributable to the study drugs.

DLT is the primary endpoint of the dose escalation portion of the study.

6.2.3. Safety Laboratory Tests

Safety laboratory tests include the following categories: hematology, blood chemistry, urinalysis, and coagulation. They will be collected at screening and frequently during the study.

Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) grades will be assigned programmatically to the laboratory test data, as appropriate.

See Appendix 1 for definition of baseline safety laboratory values.

6.2.4. Electrocardiogarm Endpoints

For **Arms A and B**, ECG endpoints will be obtained at Screening, Cycle 1 Day 2, and Cycle 2 Day 1.

For **Arm C**, ECG endpoints will be collected at screening, Cycle 1 Day 2, Cycle x Day 1 (x>1), and the end of treatment.

For **Arm B expansion**, ECG endpoints will be Screening, Day 1 of all Cycles (pre-PF-05212384 infusion and immediately prior to completion of PF-05212384 infusion), and End of Treatment Visit.

ECG endpoints include heart rate (HR), RR, PR, QRS, and QT. Fridericia's correction of QT interval (QTcF) will be calculated programmatically as $QT/(RR)^{1/3}$. If QTc is reported by sites on CRF, it will be designated QTc. Other corrections for QT interval may be considered if necessary.

See Appendix 1 for definition of baseline ECG values.

6.2.5. Left Ventricular Ejection Fraction

Left ventricular ejection fraction (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.

LVEF may be measured by either echocardiogram (ECHO) or multi-gated radionuclide study (MUGA). However, all values for a patient should be from the same method.

See Appendix 1 for definition of baseline LVEF values.

6.2.6. Vital Signs

Vital signs will be obtained at screening and frequently during the study.

6.2.7. ECOG Performance Status

Performance status will be obtained at screening and frequently during the study.

See Appendix 1 for definition of baseline ECOG values.

6.2.8. Pregnancy Test

For female patients of childbearing potential, serum or urine pregnancy test will be performed twice prior to starting study treatment and repeatedly while on study.

6.3. Other Endpoints

6.3.1. Baseline Characteristics

The baseline characteristics include:

- Age;
- Sex;
- Race;
- Height;
- Weight;
- Performance status;
- Primary diagnosis;

- Time from [histopathological] diagnosis to first dose of treatment;
- Number of prior systemic therapies;
- Number of prior surgeries;
- Prior radiotherapy (yes/no);
- Measurable disease (lesions) present (yes, no);
- Involved disease sites.

6.3.2. Treatment Administration

Duration of treatment = date of last dose – date of first dose +1.

A dose reduction is a decrease in the prescribed dose.

Missed dose (**dacomitinib only):** A missed dose is an occurrence of total daily dose of 0 mg during treatment starting from Cycle 1 Day 1. If "the total number of doses missed on UNKNOWN dates" is >0, missed doses are also indicated and should be counted towards the total number of missed doses.

Missed dose (PF-05212384, irinotecan, cisplatin): A missed dose is a 0mg total daily dose for a protocol planned dosing day. In the event that a dosing record is recorded as "Not Done", this will be considered as a missed dose.

6.3.3. Pharmacokinetic Endpoints

Blood samples for PK analysis will be taken according to the Schedule of Study Treatment and Pharmacokinetic Assessments described in the protocol.

Table 3 shows the PK parameters that will be calculated for PF-05212384, docetaxel, cisplatin, and dacomitinib from the plasma concentration-time data using standard non-compartmental methods.

Table 3. Pharmacokinetic Parameters to Be Calculated

Plasma PF-05212384 (Arms A, B, and C)

PK Parameter	Lead-in** (single dose)	Cycle 2, Day 1 (steady state)
AUC_{inf}*	X	
AUC_{last}	X	
AUC_{τ}	X	X
C_{max}	X	X
T_{max}	X	X
C_{min}		X
C_{av}		X
$t_{1/2}$*	X	X
CL*	X	X
V_{ss}*	X	X
R_{ac}		X

* If data permit.
** Lead-in = 7 days prior to Cycle 1 in Arms A and B of the dose escalation; 14 days prior to Cycle 1 in Arm C of the dose escalation. PK will be obtained for PF-05212384 on Cycle 1 Day 1 and Cycle 2 Day 1 in the Expansion Phase of B2151002.

Plasma Docetaxel (Arm A), Cisplatin (Arm B), and Dacomitinib (Arm C)

PK Parameter	Arm A Plasma Docetaxel (single dose)	Arm B Plasma Cisplatin (single dose)	Arm C Plasma Dacomitinib (steady state)
AUC_{inf}*	x	x	
AUC_{last}	x	x	
AUC_{τ}			x
C_{max}	x	x	x
T_{max}	x	x	x

* If data permit.
Note: Parameters to be calculated for Cycle 1 Day 2 and Cycle 2 Day 1. PK will not be obtained for Cisplatin in the Expansion Phase of B2151002.

6.3.4. Molecular Profiling Biomarker Endpoints

For dose escalation CCI [redacted] all patients will be required to provide an archived tumor biopsy FFPE sample. If an archived tumor sample is not available, patients must consent to provide a fresh biopsy FFPE for purpose of this analysis.

Endpoints include gene mutation status (eg, presence or absence of mutations (ie, PI3KCA/KRAS/BRAF) as well as specific mutation(s) found such as *KRAS* G12D).

CCI [redacted]

6.3.5. Expression Biomarker

Fresh FFPE tumor biopsies will be requested at Screening and on Cycle 2 Day 8 for all patients in the dose escalation, and are mandatory for patients in the MTD cohort in Arm C and for patients assigned a preliminary MTD in Arms A and B dose escalation. Optional tumor biopsies are also collected at the End of Treatment visit.

6.3.6. Serum Pharmacodynamic Endpoints

These endpoints are blood chemistry tests to be used for pharmacodynamic assessment. They include the following: serum glucose, insulin, and HbA1c, typically expressed as units/mL, or some variation thereof. These are collected at baseline (within 14 days of first dose) and multiple times on study.

6.3.9. Patient Reported Outcomes

Patient reported outcomes of functioning, global quality of life and breast cancer symptoms will be assessed using the EORTC QLQ-C30 and its breast cancer module EORTC QLQ-BR23

Patients will complete each instrument at pre-dose for the following time points: baseline, on Day 1 and Day 8 of cycles 1 and 2, on Day 1 of each subsequent cycle starting with Cycle 3, and then at the end of treatment visit. Completed questionnaires are always considered source document and must be filed accordingly.

6.3.9.1. EORTC QLQ-C30

The EORTC-QLQ-C30 (see Protocol Appendix 10) is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, emotional, cognitive, and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global quality of life (QOL) subscale, and six single item symptom scales assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and the financial impact of cancer). The questionnaire employs 4-point Likert scales with responses from "not at all" to "very much" for most of the items and 7-point Likert scales for global health and overall QOL.[6] Responses to all items are then converted to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning/QOL. For symptom-oriented scales, a higher score represents more severe symptoms. A 10-point or higher change in scores from baseline is considered clinically significant.

6.3.9.2. EORTC QLQ-BR23

The EORTC-QLQ-BR23 (see Protocol Appendix 11) is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and four symptom scales (systemic side effects, breast symptoms, arm symptoms, upset by hair loss).

The subscales of the EORTC QLQ-C30 and the QLQ-BR23 will be scored based on the EORTC scoring manual.[7] Scales will utilize all completed items to derive the score of each scale. For the EORTC QLQ-C30 and BR-23 in cases where two answers are given to one item, the more severe answer will be counted. If less than half of the constituent items on the QLQ-C30 and QLQ-BR 23 have been answered for a multi-item subscale, that subscale will be considered missing. Single-item subscales will be considered missing if the constituent item is incomplete

In summary, each scale of the EORTC QLQ-C30 and the QLQ-BR23 will be transformed so that scale scores will range from 0 to 100. The transformation will proceed in two steps. First, the average of the items contributing to a subscale will be calculated to compute the raw score of the scale. Next, a linear transformation will be applied to 'standardize' the raw score. After scores are transformed, higher scores on the EORTC QLQ-C30 or the QLQ-BR23 will represent higher ("better") levels of functioning and/or a higher ("worse") level of symptoms.

6.4. Covariates

N/A

7. HANDLING OF MISSING VALUES

7.1. Conventions for Missing Dates

In compliance with Pfizer Data Standards (PDS), if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of resolution cannot be prior to date of onset; if replacing resolution date with the 1st of the month results in a negative

duration, the resolution date will be set to the onset date). Similarly, if the month and day of the month are missing for any date used in a calculation, the 1st of the month of January will be used to replace the missing date unless the calculation results in a negative time duration.

For adverse events, onset date and stop date will be imputed based on the PDS standard algorithms to ensure that if the onset date is missing for an AE, the AE is considered to be treatment emergent unless the collection date is prior to the treatment start date.

7.2. Missing Tumor Assessments

If baseline tumor assessment is inadequate, the patient cannot be assessed for response. See Appendix 1 for definition of adequate baseline tumor assessment.

If measurements for one or more target lesions are missing for an evaluation, the objective status for that evaluation is Indeterminate.

If non-target disease was not assessed, then a patient who qualifies for an objective status of CR based on target disease will be classified as PR. Otherwise, missing non-target disease assessments generally do not affect response determination. Such cases will be reviewed carefully by the clinical team.

Patients who do not have post-baseline tumor assessments and present with early death due to disease or early progression (ie, prior to first planned post-baseline tumor assessment) will be assigned a best response of PD.

Patients who come off trial early (prior to first **planned** post-baseline assessment) for reasons other than PD (early toxicity, withdrew consent, etc.) will be considered evaluable and Indeterminate for tumor response.

7.3. Missing Data in Safety Endpoints

There will be no imputation of missing data for any safety endpoints other than those explicitly specified.

The percentage of patients with an adverse event will be calculated using the number of patients in the safety analysis set as the denominator, regardless of whether there are missing data for AEs.

The denominator for summary tables for each laboratory test will be all patients in the safety analysis set with at least one evaluable cycle for that test. Different laboratory tests may have different denominators, depending on the number of evaluable patients for each test. An evaluable cycle is any cycle with at least one assessment of that test.

7.3.1. Missing QTc Data

For analyses using the QTc analysis set, no values will be imputed for missing data except for averaging of triplicate measurements. If one or two of the triplicate measurements for an ECG endpoint are missing, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing at a time point for an ECG endpoint, no values will be imputed for this time point.

7.3.2. Missing Left Ventricular Ejection Fraction Data

For shift table summary or analysis of changes from baseline, the data for each patient must be derived from the same technique (echocardiogram [ECHO] or multi-gated radionuclide study [MUGA]). Even though alternative techniques may be used for confirmation of results, all data for summaries must be derived from the technique used for baseline LVEF assessment.

7.4. Missing Pharmacokinetic Data

7.4.1. Concentrations Below Limit of Quantification

In all data summaries and figures, concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

7.4.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if one of the following cases is true:

- A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
- A deviation in sampling time is more than 10% from the nominal time or a concentration has been flagged anomalous by the pharmacokineticist.

7.4.3. Pharmacokinetic Parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses.

If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a patient discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular arm with N less than 3. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due, for example, to an unexpected event such as vomiting before the drug is completely absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

7.5. Missing Patient Reported Outcome Data

For the QLQ-C30 and QLQ-BR23 in cases where two answers are given to one item, the more severe answer will be counted. For QLQ-C30 and QLQ-BR23, if at least half of the constituent items for the multi-item functional or symptom scale have been answered, then the score for that scale may be pro-rated based on the non-missing items. Missing scale scores will not be imputed but considered missing for analysis purposes.

7.6. Missing Biomarker Data

Patients with no biomarker results are not included in the biomarker analysis. Patients with missing baseline biomarker assessment are not assessable for baseline description, for the examination of association with other endpoints, or for assessment of change from baseline. Patients missing follow-up biomarker assessments are not assessable for change from baseline. No missing pharmacodynamic or tumor biopsy data will be imputed.

If an archival or fresh baseline tumor sample is missing, the patient cannot be assessed for genetic variations at baseline.

7.6.1. Handling of Duplicate Biomarker Data

Duplicate biomarker data for a visit are not expected. However, if duplicate data for a visit are assayed by the vendor, the statistician will provide instructions to the programmer as to which, if any, record is to be used for analysis. A flag will be included in the database indicating which record (if any) is selected for analysis.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Standard statistical methods will be used for different types of variables:

- Continuous: mean, standard deviation, median, and range;
- Time-to-event: Kaplan-Meier estimate of survivor function, median time to event, Brookmeyer-Crowley confidence interval for median time to event, probability of event by a particular time point, log(−log) method with back transformation for confidence interval of estimated probability of event by a given time point;
- Categorical: count and percentage of each category, confidence interval of the percentage based on normal approximation (or exact method if so specified);
- Pearson's correlation coefficient will be calculated for two continuous variables if their linear relationship is of interest;
- For biomarker 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 by timepoint, as appropriate. For each pair of specimens, the ratio-to-baseline or percent change of these same parameters will also be calculated.

In general, data will be summarized by arm, with the Arm B expansion summarized separately.

8.2. Statistical Analyses

Refer to Section 5 for definitions of analysis sets.

8.2.1. Analyses of Primary Endpoint

8.2.1.1. Dose escalation

Analysis set: Per protocol analysis set.

DLT is the primary endpoint.

The number of patients with DLTs will be summarized by dose level for each arm. The number of patients with DLTs will also be summarized by dosing cohort for each arm.

A DLT listing will be provided by arm, which is a listing of the adverse events flagged as DLTs.

8.2.1.2. Arm B Expansion

Analysis set: Response analysis set

Objective Response is the primary endpoint.

Objective response (CR + PR) will be summarized by count and percentage and a 95% exact confidence interval (CI) for the objective response rate will be provided by arm.

Best overall objective response will be summarized for each arm by count and percentage for each category as defined in Section 6.1.3.

8.2.2. Analysis of Safety Endpoints

Analysis set: Safety analysis set (unless indicated otherwise)

Summaries for safety endpoints will be by dose escalation arm, dose level, and Arm B expansion arm.

8.2.2.1. Summaries of Adverse Events

The frequency of adverse events will be computed by counting each patient only once per MedDRA preferred term grouped by system organ class and according to the maximum NCI CTCAE grade attained by the patient over the specified period. The percentage of patients with an event will be calculated using the number of patients in the safety analysis set as the denominator.

Treatment-related AEs will be summarized in two ways (Arms A and B) or three ways (Arm C) based on the study drug(s) that the AE is attributed to:

- All treatment-related AEs;
- PF-05212384-related AEs;
- Dacomitinib-related AEs (Arm C only).

If a treatment-related AE is not attributed to any specific drug, it will be included in the summaries of PF-05212384-related AEs (all arms) and dacomitinib-related AEs (Arm C only).

The following summaries will be presented for all-causality and treatment-related treatment-emergent AEs separately.

An overall summary of treatment-emergent AEs will be presented with the following counts:

- number of patients evaluable for AEs;
- total number of AEs (counting each unique preferred term across all patients);
- total number of SAEs (counting each unique preferred term across all patients);
- number of patients with AEs;
- number of patients with SAEs;
- number of patients with Grade 3 or Grade 4 AEs;
- number of patients with Grade 5 AEs;
- number of patients who discontinued due to AEs (per the AE CRF page);
- number of patients with dose decreases due to AEs (per the AE CRF page);
- number of patients with dose delays due to AEs (per the AE CRF page).

The number and percentage of patients with treatment-emergent AEs will be summarized by MedDRA system organ class, preferred term, and maximum CTCAE grade by arm and dose level for all cycles combined. The total for all grades will be included as the last column. The same summary will also be presented separately for AEs in lead-in period, AEs in Cycle 1 and AEs in Cycles beyond Cycle 1.

The number and percentage of patients with treatment-emergent AEs will be summarized by MedDRA preferred term and maximum CTCAE grade in descending order of frequency (based on total frequency for all grades) by arm and dose level for all cycles combined. The total for all grades will be included as the last column. The same summary will also be presented separately for AEs in lead-in period, AEs in Cycle 1 and AEs in Cycles beyond Cycle 1.

The number and percentage of patients with treatment-emergent **SAEs** will be summarized by MedDRA system organ class, preferred term, and maximum CTCAE grade by arm and dose level for all cycles combined. The total for all grades will be included as the last column. The same summary will also be presented separately for AEs in lead-in period, AEs in Cycle 1 and AEs in Cycles beyond Cycle 1.

The number and percentage of patients with treatment-emergent **AEs of Grade 3-5** will be summarized by MedDRA preferred term and maximum CTCAE grade in descending order of frequency (based on total frequency for all grades) by arm and dose level for all cycles combined. The total for all grades will be included as the last column. The same summary will also be presented separately for AEs in lead-in period, AEs in Cycle 1 and AEs in Cycles beyond Cycle 1.

Additional tables may be provided by grouping AEs of different CTCAE grades.

8.2.2.2. Analyses of Laboratory Tests

The percentage of patients experiencing laboratory test abnormalities will be calculated using the number of patients in the safety analysis set with at least one evaluable cycle for that laboratory test as the denominator.

The number and percentage of patients experiencing laboratory test abnormalities will be summarized according to worst CTCAE grade by laboratory test for each arm and dose level. The total for all grades will be included as the last column. Separate tables will be generated for hematology, coagulation, chemistry, and urinalysis laboratory tests. The same summaries will also be presented separately for laboratory tests in lead-in period, those in Cycle 1 and those in Cycles beyond Cycle 1.

Shift tables will be presented for baseline grade to worst post-baseline grade by laboratory test for selected CTCAE graded hematology, coagulation, chemistry, and urinalysis laboratory tests for each arm and dose level, provided that there are at least 7 patients with non-missing baseline values at a dose level of an arm. The total for all grades will be included as the last row and the last column. One table will be generated for each category of safety laboratory tests (hematology, coagulation, chemistry, and urinalysis).

For laboratory tests without CTCAE grade definitions, the number and percentage of patients with laboratory tests meeting the criteria of abnormalities will be summarized for each arm and dose level by laboratory test according to worst post-baseline results for normal baseline, abnormal baseline and without regard to baseline, as appropriate.

Incidence and non-CTCAE abnormality criteria (for non CTC graded labs) of hematology labs, coagulation labs, chemistry labs, and urinalysis labs for all cycles (Normal, Abnormal Low, and Abnormal High).

8.2.2.3. Hy's Law Listing

A listing will be provided for patients who potentially meet Hy's law criteria. Dates and results for total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) will be presented according to arm and dose level for all patients.

8.2.2.4. Analyses of Electrocardiogram Endpoints

Analysis Set: QTc analysis set

At each time point, for each ECG endpoint, data for a patient will be averaged. All summary statistics and data presentations will use these averaged data. Any data obtained from ECGs repeated for safety reasons after a nominal time point will not be averaged with the values obtained at the preceding nominal time point. Interval measurements from these repeated ECGs will be included in the outlier analysis as individual values obtained at unscheduled time points, if unplanned ECGs are done in triplicates or duplicates the values will be averaged.

A summary of ECG endpoints (HR, RR, PR, QRS, QT, and QTcF) will be provided by arm and dose level for each time point (n, mean, standard deviation, median, min, and max).

A shift table will be provided by arm and dose level for ECG abnormality on treatment vs baseline (yes, no, not done) for any dose level for which there are at least 7 patients with non-missing values at baseline. Unevaluable results will be grouped with "not done."

The following summaries will be based on QTcF only.

Change from baseline will be summarized for QTcF by arm and dose level: baseline and change from baseline at each time point (n, mean, standard deviation, median, min, and max).

For each patient, the maximum (worst) post-baseline value and the maximum increase from baseline will be calculated across all post-baseline time points.

Categorical analysis (outlier analysis) of the data will be conducted and summarized by arm and dose level with the following categories:

- Number of subjects with maximum increase from baseline in QTcF (≤30, >30-60, and >60 ms);
- Number of subjects with maximum post-baseline QTcF (<450, 450-480, >480-500, and >500 ms).

A shift table of QTcF from baseline to worst post-baseline value will be provided by arm and dose level with QTcF categories based on CTCAE grades (<450, 450-480, >480-500, and >500 ms).

Additional concentration-QTcF analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

Summaries of corrected QT intervals based on other methods may be presented as appropriate. If corrected QT intervals are reported on the CRF (QTc), they will not be summarized, but will be included in the listing of ECG data.

8.2.2.5. Left Ventricular Ejection Fraction (Arm C Only)

A shift table of LVEF from baseline to worst post-baseline value will be provided by dose level with LVEF categories of <45%, 45%-<50%, 50%-<55%, and ≥55%. Worst post-baseline value will be calculated as the minimum LVEF across all post-baseline time points. "Not reported" may be included as a category.

Change from baseline will be summarized for LVEF by dose level: baseline and change from baseline at each time point (n, mean, standard deviation, median, min, and max).

8.2.2.6. Listings for Safety Endpoints

All safety endpoints including AEs, laboratory tests, ECOG performance status, ECG, LVEF, physical examinations, and vital signs will be listed. Where appropriate, changes from baseline to each assessment will be included. In the listing of AEs, TEAEs will be flagged.

Selected subsets of AEs will also be listed separately. These include Grade 3-5 AEs (all causality and treatment related), SAEs (all causality and treatment related), SAEs per the safety database, treatment related SAEs with onset after 28 days from the last dose of study treatment, discontinuations due to AEs (all causality and treatment related), temporary discontinuations and dose reductions due to AEs (all causality and treatment related), all AEs for patients off treatment "due to AE" on subject summary page at the end of treatment, all AEs for patients coded as "permanently discontinued" on AE page.

Physical exam for screening and changes from screening will be listed.

Selected subsets of laboratory tests may also be listed separately, including Grade 3-5 laboratory tests, abnormal laboratory tests without CTCAE grades. Laboratory tests abnormalities by test and subject.

A listing of deaths will be presented for patients who die while on treatment or within 28 days of permanent discontinuation of treatment (patient id, treatment stop date, progression date, date of death, cause of death). In addition, a listing of deaths will be presented for all patients who die on study.

8.2.3. Analyses of Study Conduct

Analysis set: Full analysis set

Summaries will include the following:

- Summary of patient accrual by center and arm;
- Summary of patient evaluation by arm: Number and percent enrolled, treated, assessed for adverse events, assessed for laboratory tests, and assessed for efficacy;
- Summary of discontinuation from study by arm.

Listings will include the following:

- Listing of patients enrolled but not treated;
- Listing of inclusion and exclusion criteria deviations;
- Listing of patients excluded from each analysis set, including the reason for the exclusion.

8.2.4. Analyses of Baseline Characteristics

Analysis set: Safety analysis set

8.2.4.1. Demographic Characteristics and Primary Diagnosis Related Characteristics

Patient baseline characteristics at study entry, as listed in Section 6.3.1, will be summarized by arm (Arm A, B, and C of the dose escalation and Arm B expansion arms).

Demographic summary will include descriptive statistics for age, race, weight, and height by sex (male, female, and total). Age will be summarized by age group (number and percentage) and as a continuous variable (mean, SD, median, range).

ECOG performance status at baseline will be summarized by arm with number and percentage for each status.

Summary of disease history will include primary diagnosis (number and percentage), and time from diagnosis to enrollment (median and range).

Summary of prior treatment for cancer under study will include prior radiotherapy (yes/no), prior surgeries (yes/no), number of prior systemic therapies (number and percentage for 0, 1, 2, etc.).

Summary (and listing) of historical molecular biology of disease data will include the marker data from the primary diagnosis page.

Patient disease will be summarized with respect to current disease stage (if appropriate), organ sites of disease (if appropriate), number of sites of disease (based on baseline assessment CRF page), and measurable disease (yes/no) for each primary diagnosis by arm.

Listings will be provided for baseline data from which the above summaries are generated.

8.2.4.2. Medical History

Relevant medical history findings will be summarized as past or present by arm. If both past and present history findings are present for a condition, a patient will be counted under present history only.

A listing of medical history will be provided.

8.2.4.3. Prior Drugs Taken and Prior Non-Drug Treatment

The number of patients who took prior drug treatments will be summarized by arm for drug treatments which were taken before first day of treatment but within 28 days of first dose of study treatment. All prior drug treatments within the window will be included, whether or not they continue during treatment.

The number of patients who took prior non-drug treatments will be summarized by arm for non-drug treatments which were taken before first day of treatment but within 28 days of first dose of study treatment. All prior non-drug treatments within the window will be included, whether or not they continue during treatment.

Listings of prior drug and non-drug treatments will be provided.

8.2.5. Treatment Descriptions

Analysis set: Safety analysis set

8.2.5.1. Treatment Administration

The number and percentage of patients on treatment and off treatment for each reason will be presented by arm and dose level.

Treatment administration will be summarized for each drug and for overall (either or both of the two drugs), as appropriate, by arm and dose level:

- Number (%) of patients starting lead-in period, 1, 2, 3, 4, 5+ cycles for each drug and for overall;
- Number of cycles started (median, minimum, maximum) for each drug and for overall;
- Summary of duration of treatment (days) for each drug and for overall;
- Summary of days dosed: only days with dosing are counted;
- Summary of total dose prescribed (sum of all prescribed doses on dosing records) and total dose administered (sum of all actual administered doses on dosing records) by drug;
- Number (%) of patients with at least one dose reduction for each drug and for overall; for each drug, further divided into 1 reduction and ≥2 dose reductions;
- Number (%) of patients with at least one missed dose which may be further broken down into 2 or more categories;
- Number (%) of patients with at least one delayed cycle;
- Number (%) of patients with infusion rate change (broken down by due to Adverse Event and due to Other reason) – IV drugs only;
- Number (%) of patients with infusion interruption (broken down by due to Adverse Event and due to Other reason) – IV drugs only;
- Number (%) of patients with any dose change (broken down by due to Adverse Event and due to Other reason) – dacomitinib only.

A summary listing will be provided that will include all patient-level variables summarized above.

Treatment administration in terms of relative dose intensity will be summarized **by cycle and overall** for each arm and dose level as below:

- Cumulative dose received and percent of planned dose (the initial prescribed dose for the study prior to any dose reduction) for each drug.

- Relative Dose (RD) Intensity by cycle: [cumulative dose in the cycle]/[intended cumulative dose per cycle] x 100. The intended cumulative dose is constant for all cycles being fixed at the start of treatment.

- Overall RD: [overall cumulative dose]/[intended cumulative dose per cycle x number of cycles] x 100. The intended cumulative dose is constant for all cycles being fixed at the start of treatment.

A cycle-level listing will be presented by arm and dose level, which will include cycle number (starting from lead-in, if applicable), cycle start date, study day, cycle length, delayed from previous cycle (y/n), total dose received for each drug, and percent of planned dose for each drug.

Dosing records will be listed.

8.2.5.2. Concomitant Medications and Non-Drug Treatments

Concomitant and non-drug treatments refer to all drug and non-drug treatments received while on active treatment, whether or not they are recorded as prior treatments.

A summary of concomitant drug and non-drug treatments may be provided.

8.2.6. Analyses of Pharmacokinetics

8.2.6.1. Pharmacokinetic Concentrations

Analysis set: PK concentration analysis set

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), steady-state volume of distribution V_{ss}, and the observed accumulation ratio (R_{ac}) will also be estimated.

For PF-05212384, docetaxel, cisplatin, and dacomitinib, concentrations will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time for each arm and each drug. 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 for each arm and each drug. Median profiles will be presented on both linear-linear and log-linear scales.

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

8.2.6.2. Pharmacokinetic Parameters

Analysis set: PK parameter analysis set.

To assess the pharmacokinetics of PF-05212384, docetaxel, cisplatin, and dacomitinib, the PK parameters detailed in Section 6.3.3 will be listed and summarized for patients in the PK analysis set (as defined in Section 5.4.3). Missing values will be handled as detailed in Section 7.4. Each PK parameter will be summarized by arm and day and will include the set of summary statistics as specified in the table below:

Table 4. Summary Statistics to Be Calculated for Pharmacokinetic Parameters

Parameter	Summary statistics
AUC_{last}, AUC_{inf}*, C_{max}, CL* and Vss*	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum, geometric mean, geometric CV%
$t_{1/2}$*	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum
T_{max}	N, median, minimum, maximum

*=if data permit

8.2.7. Analyses of Additional Efficacy

8.2.7.1. Dose Escalation

Analysis set: Response analysis set

There are two subsets for the dose escalation:

1. All patients; and,
2. Patients with measureable disease only.

Best objective overall response (OR) and CBR will be summarized with count and percentage for each category by arm. If data permit, OR and CBR summaries may be further broken down by tumor type (and dose level) within each arm.

Waterfall plots will be presented by arm for maximum percent change in tumor size (sum of diameters) from baseline, with selected characteristics such as tumor type, dose level and/or best overall response identified.

8.2.7.2. Expansion

Analysis set: Response analysis set

CBR will be summarized with count and percentage by arm.

Duration of response will be calculated for patients with an objective response (CR or PR). The median duration of response will be estimated using Kaplan-Meier method for each arm. A 95% CI for the median of each arm will be provided using the Brookmeyer-Crowley method.

A patient listing for duration of response will be provided and it will include: patient identification, treatment arm, first objective response date and study day of objective response, date and study day of last objective response, date of progression, censoring date, duration of response, and censoring reason.

Waterfall plots will be presented by expansion arm for the best percent change in tumor size (sum of diameters) from baseline, the largest decrease or smallest increase.

PFS will be listed by arm. If data permit, the median PFS and its 95% confidence interval using the Brookmeyer-Crowley method will be presented.

Posterior probabilities using a non-informative Jeffrey's prior and various true response rates will be used to calculate the probability of not being inferior to the true response rate given the expansion data observed.

8.2.7.3. Listings of Efficacy Endpoints for All Patients

All patients will be included in the listings. As appropriate, footnotes will be applied to indicate inclusion in the response analysis set.

A listing of target lesion measurements, sum of diameters at each assessment, change from baseline and nadir, and investigator assessments will be provided.

A listing of efficacy to include arm, tumor type, dose level, date of enrollment, measurable disease (y/n), first treatment (lead-in drug, dose, and date), Cycle 1 Day 1 treatment (drugs, doses, and day [relative to first dose of treatment]), day of last treatment, best overall response, day of first CR [at an evaluation], most recent day of CR [at an evaluation], first day of PR [at an evaluation], most recent day of PR [at an evaluation], day of progression, day of decision to discontinue treatment, reason off treatment, day of death or last contact (if available), and cause of death (if applicable). Day is relative to first dose of treatment: day = date of event − date of first dose + 1.

A tumor assessment listing will be provided by arm, tumor type, dose level and patient for each cycle, which will include: tumor assessments (target lesions [excluding lymph node target lesions], non-target lesions, lymph node target lesions, and new lesions), and the investigator overall objective tumor assessment.

8.2.8. Patient Reported Outcomes

Analysis of the PRO endpoints will be based on the PRO analysis set. The PRO analysis endpoints will be based on the instruments QLQ-C30 and QLQ-BR 23. For each treatment group and at each time point, the number and percentage of patients who completed these instruments will be summarized, as will the reasons for non-completion of these measures. An instrument is considered completed if at least one item was answered by the patient.

EORTC QLQ-C30

This questionnaire contains 30 questions organized into 5 multi-item functional scales, 3 multi-item symptom scales, a global quality of life scale, and 6 single item symptom scales. For each of the 15 scales, the results will be summarized using means (and standard deviation), 95% confidence interval, and medians (and range) for each arm at each time point. This will be done based on the observed values as well as changes from baseline within the arm.

For each of the 15 scales, a graphical display of means over time as well as mean changes from baseline over time will also be provided.

EORTC QLQ-BR23

This questionnaire contains 23 questions organized into 4 functional scales and 4 symptom scales. As with C30, the analysis of the BR23 scales will consist of descriptive statistics on means and changes from baseline. Also, as with C30, graphical displays of means and changes from baseline over time will also be provided for each BR23 scale.

Patients will be classified as "improved," "stable," or "deteriorated" according to a 10-point or greater change in score as this change is perceived by patients as being clinically significant on the EORTC QLQ C30.[5,8] Improved will be defined as at least a 10-point change in a "good" direction, deteriorated as at least a 10-point change in a "bad" direction, and stable if the patient neither improved nor deteriorated.

In addition to the change from baseline in scores, the proportion of patients whose scores improved, deteriorated, or remained stable over treatment will be evaluated with the PRO evaluable population.

In addition to the above analyses, an examination of the time to deterioration (TTD) will be carried out using survival analysis methods including Kaplan Meier plots. Deterioration will be defined as a decrease of a pre-specified number of points based on MID (minimal important difference). This analysis will be carried out for the variable Global Health Status/QoL and an MID of 10 points will be used.

8.2.9. Analysis of Biomarkers

Analyses of biomarkers are secondary for the dose escalation phase [redacted]

8.2.9.1. Analyses of Molecular Profiling Biomarkers

Analysis Set: Molecular profiling tumor analysis set.

8.2.9.1.1. Molecular Biomarkers

Dose escalation and expansion will be summarized separately.

A list of mutations and alterations to be summarized for the baseline tumor biopsies will be provided prior to database release (these may include KRAS, BRAF, PTEN).

Summary Analyses will include:

- Mutation and other biomarker data will be summarized by arm, tumor type, and/or dose level, if data permit.
- Associations of mutations and other biomarkers versus best overall response will be assessed (ie, count and % in each response category for each mutation or other biomarker) by arm, tumor type, and/or dose level, if data permit.
- A summary of demographics will be produced by arm if the sample size of the molecular profiling tumor analysis set is less than 80% of the total sample size for any arm:
    - Data will be presented to show the copy number alteration or mutation by patient along with change from baseline in tumor size in a waterfall plot.
- A listing of biomarkers by arm will be produced: all biomarker data collected will be listed. Patients included for summaries with best overall tumor response will be flagged.

For assessment of associations with best overall response, only those patients who are part of the molecular profiling tumor analysis set and the response analysis set will be included. For other summaries, all patients in the molecular profiling tumor analysis set will be included.

8.2.9.2. Analyses of Expression Biomarkers

Analysis set: Expression tumor analysis set

[redacted]

For paired fresh tumor biopsies, time points consist of Screening (baseline), and C2D8 [redacted]. A list of proteins and corresponding antibody epitopes to be summarized will be provided prior to database release (these may include pAkt, pErk).

Analyses will include:

- Baseline, C2D8 [redacted] and ratio of C2D8 [redacted] to baseline will be summarized. Paired C2D8 [redacted] and baseline data will be analyzed using Wilcoxon signed-rank test by arm, tumor type, and/or dose level if the number of pairs is at least 10;
- A summary of ratio of C2D8 [redacted] to baseline, as well as baseline and C2D8 [redacted] stand-alone biomarker value, versus best overall response will be provided by arm and dose level, if data permit;
- A summary of demographic and baseline characteristics will be produced if the sample size of the expression tumor analysis set is less than 80% of the total sample size for any arm. The characteristics to be summarized will be selected before database release:

- Plots of percent inhibition of phosphor-protein will be provided. The plot will include a bar for each protein with the patient value, the median value, and the minimum and maximum values of the population. Proteins may include pAkt, pErk, as well as others.

- A listing of protein data by arm will be produced: all biomarker data collected will include a flag indicating inclusion in summaries with overall best tumor response.

For the summaries of ratio of C2D8 CCI to baseline versus best overall response, only those patients who are part of the expression tumor analysis set and the response analysis set will be included. For other summaries, all patients in the expression tumor analysis set will be included.

8.2.9.3. Analyses of Serum Pharmacodynamic (PD) Biomarkers

Analysis set: Serum PD analysis set

Dose escalation and expansion will be summarized separately.

PD biomarkers (including serum glucose, insulin, and HbA1c) are measured at screening (baseline) and multiple time points post baseline (including C1D8, C1D15, C2D1, C2D15, and EoT). Baseline is defined as the last measurement prior to dosing, which is the measurement at screening or the C1D1 pre-dose measurement if collected:

- Baseline, CxDy, and ratio of CxDy to baseline, as appropriate, will be summarized. Paired data (CxDy and baseline data) will be analyzed using Wilcoxon signed-rank test, by arm, tumor type, and/or dose level, for time points at which the number of pairs is at least 10;

- A summary of baseline and ratio of CxDy to baseline versus best overall response will be provided, by arm and by dose level, if data permit;

- Spaghetti plots and box plots for each biomarker will be provided, by arm and dose;

- A listing of PD biomarkers by arm will be produced.

For the summary of ratio of CxDy to baseline versus best overall response, only those patients who are part of the serum PD analysis set and the response analysis set will be included. For other summaries, all patients in the serum PD analysis set will be included.

CCI

CCI

[redacted]

9. REFERENCES

1. 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.

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

3. Huang X, Biswas S, Oki Y, Issa JP, Berry DA. A parallel Phase I/II clinical trial design for combination therapies. Biometrics. 2007;63(2):429-436.

4. Oron AP, Azriel D, Hoff PD. Dose-finding designs: the role of convergence properties. International Journal of Biostatistics. 2011; 7(1):1–17.

5. Osoba D et al, Interpreting the significance of changes in health related quality of life scores. J. Cin Oncology. 1998. 16:139-144.

6. Aaronson NK 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 85:365-76, 1993

7. Fayers P, Bottomley A. Quality of Life Research within the EORTC – The EORTC QLQ-C30, on behalf of the EORTC Quality of Life Group. European Journal of Cancer. 38 (Suppl4):125-133, 2002.

8. Fayers P et al. EORTC QLQ-C30 Scoring Manual. 2001. EORTC, Brussels.

10. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Appendix 1.1. Definition and Use of Visit Windows in Reporting

Enrollment	Assignment of enrollment number, treatment arm and dose level.
Treatment start	First dose of treatment, typically the PK lead-in dose.
Planned Cycle Length	Planned cycle length is 21 days.
Day 1 of a cycle (cycle start date)	Day 1 of a cycle per Schedule of Activities. For Arm A, Day 1 of a cycle is defined as the day on which the patient receives docetaxel. For Arm B, Day 1 of a cycle is defined as the day on which the patient receives cisplatin. For Arm C, Cycle 1 Day 1 is the day on which the patient receives dacomitinib after the lead-in dose, and Day 1 for Cycles 2 and beyond is defined as the day on which the patient receives PF-05212384. For all arms, if only one drug remains being administered, Day 1 of a cycle x ($x \geq 2$) is defined as the day on which the patient receives this drug.
Cycle length (all but final cycle)	Cycle length is length from Day 1 of a cycle to the day prior to Day 1 of the next cycle.
Final cycle	For patients on treatment, from Day 1 of most recent cycle start to protocol specified cycle length. For patients withdrawn from treatment, from Day 1 of most recent cycle to 28 days post final dose.
DLT evaluation period	From the PK lead-in dose through Cycle 2 Day 1.
Baseline safety laboratory values	Baseline safety laboratory values are collected within 14 days prior to the first dose of study drug and are from a time point closest to, but prior to, start of study drug.

Baseline ECGs	Baseline ECGs are within 14 days of first dose of study drug and are from a time point closest to, but prior to, start of study drug.
Baseline LVEF	Baseline LVEF values are within 28 days of first dose of study drug and are from a time point closest to, but prior to, start of study drug.
Baseline ECOG performance score	Baseline ECOG performance scores are assessed within 14 days of first dose of study drug and are from a time point closest to, but prior to, start of study drug.
Adequate baseline tumor assessment	All required scans must be done within 28 days prior to first dose of study drug and all disease sites must be documented appropriately. The specific requirements include: • all known disease sites are assessed at baseline and documented on baseline assessment CRF; • all tumor assessments at baseline are within 28 days of first dose of study drug (baseline assessment CRF and tumor lesions CRFs); • for target lesions other than malignant lymph nodes, the longest diameter must be ≥ 10 mm by CT scan or caliper, and ≥ 20 mm by chest X-ray; • for malignant lymph nodes as target lesions, the short axis must be ≥ 15 mm by CT; • target lesions are truly measurable (non-measurable lesions are listed in RECIST v1.1 Guidelines, as adapted in Appendix 2 of the protocol); • method of assessment is reliable, eg, ultrasound is not useful in assessment of lesion size; and • description is provided for all non-target lesions.
Cycle k +1 delay	Time from Cycle k Day1 to Cycle k+1 Day 1 is greater than the planned cycle length.

Appendix 2. STATISTICAL METHODOLOGY DETAILS

Appendix 2.1. Interval Design for Arms A and B

An interval design for MTD finding assigns a dose to a new cohort of patients based on the estimated DLT rate of the current dose compared to a pre-specified interval of DLT rate.[4] In this appendix, a general interval design for a single-agent MTD finding trial (or arm) is described, followed by a description of specific implementation in Arms A and B.

A General Interval Design

Suppose that J doses of an agent are investigated in a trial (or arm). Let p_j be the probability of DLT for the *j*-th dose, *j* = 1, …, *J*. Assume monotonic dose-DLT relationship, $p_1 < p_2 < ... < p_J$. The objective of the trial is to find the dose, *s*, at which the probability of DLT is closest to the target, p_T, among all doses, $s = \text{argmin}_{1 \le j \le J} | p_j - p_T |$.

The first cohort of patients can be assigned arbitrarily to a dose. However, to protect patient safety, the dose for the first cohort of patients should be selected based on the following rule.

1. The dose assigned to the first cohort of patients is deemed highly likely to be tolerable, eg, dose 1 or dose 2.

Suppose that dose j is the current dose with which patients are treated and $n_j (n_j \ge 1)$ patients have been treated cumulatively with this dose. Of the n_j patients, $x_j (x_j \le n_j)$ patients have experienced DLTs. Let $\hat{p}_j = x_j / n_j$. Let $\Delta_L(n_j) > 0$ and $\Delta_U(n_j) > 0$ be functions of n_j such that $\left(p_T - \Delta_L(n_j), p_T + \Delta_U(n_j)\right)$ defines an interval of DLT rate. Starting from the second cohort, the dose assignment rule is as follows:

2. if $p_T - \Delta_L(n_j) < \hat{p}_j < p_T + \Delta_U(n_j)$, the next cohort of patients will be assigned to dose j again;

3. if $\hat{p}_j \le p_T - \Delta_L(n_j)$, the next cohort of patients will be assigned to dose *j*+1 (unless $j = J$ in which case dose *J* will be assigned again);

4. if $\hat{p}_j \ge p_T + \Delta_U(n_j)$, the next cohort of patients will be assigned to dose *j*−1 (unless $j = 1$ in which case dose 1 will be assigned again).

Note that in other interval designs, Δ_L and Δ_U may depend on additional parameters or may be constants. For convenience, (2) is also called "stay" or “S,” (3) is also called "escalate" or “E,” and (4) is also called "de-escalate" or “D.”

In practice, due to concern of exposing too many patients to a toxic dose, it is desirable to stop assigning patients to a dose for which cumulative data suggest to be most likely too

toxic. A Bayesian dose elimination rule can be added to the dose assignment rule for this purpose:[1,2]

5. If $n_j \geq 3$ and $\Pr(p_j > p_T \mid \text{data}) > 0.95$, then doses *j* and higher will be eliminated from further testing in the trial, and the trial will be terminated if the first dose is eliminated.

Here $\Pr(p_j > p_T \mid \text{data})$ is evaluated based on a beta-binomial model. Assuming that the number of patients experiencing DLTs, X_j, follows a binomial distribution (with size and probability parameters n_j and p_j) and p_j has a prior distribution of beta(1,1), then the posterior distribution of p_j is beta$(1+x_j, 1+n_j-x_j)$.

Typically, a trial using an interval design ends when it reaches the planned sample size or when the lowest dose is eliminated due to the dose elimination rule. Additional considerations may be added.

At the end of the trial, isotonic estimates of DLT rates are calculated and used as the basis for the selection of estimated MTD:[1,2] select as the estimated MTD the dose for which the difference between the isotonic estimate of DLT rate and p_T is the smallest among all tested doses, ie, $\tilde{s} = \text{argmin}_{1\leq j\leq J} \mid \tilde{p}_j - p_T \mid$, where dose $\tilde{s}$ is the estimated MTD, and $\tilde{p}_j$ is an isotonic estimate of p_j. If two or more doses share the same isotonic estimate of DLT rate, then the estimated MTD will be the highest dose in the case that the isotonic estimate is lower than p_T, and the lowest dose in the case that the isotonic estimate is greater than p_T.

Implementation in Arms A and B

The doses available for each are arm are listed in Table 1.The target DLT rate is $p_T = 0.25$. The first cohort of patients will be treated with dose levels A1 and B1, respectively. As of July 2014, dose levels A1 and A2 and B1, B2, and B3 have been tested and found to be tolerated without DLTs. The starting dose level for the purposes of the simulations is A1 and B1 with 8 dose levels expected to be administered.

For $2 \leq n_j \leq 4$, dose assignment will be based on the mTPI method with $p_T = 0.25$ and equivalence interval of [0.20, 0.32], which can be viewed as an interval design with $\Delta_L(n_j)$ and $\Delta_U(n_j)$ in the table below; for $n_j \geq 5$, $\Delta_L(n_j) = 0.051$ and $\Delta_U(n_j) = 0.071$ are selected so that an observed DLT rate in [0.20, 0.32] will result in a dose assignment of "Stay" for $5 \leq n_j \leq 25$.

n_j	2	3	4	≥ 5
$\Delta_L(n_j)$	0.10	0.10	0.10	0.051
$\Delta_U(n_j)$	0.26	0.15	0.10	0.071

For ease of use, rules (2)-(5) specific to Arms A and B are presented in a matrix of E/S/D/DU for all possibilities of x_j for $2 \le n_j \le 15$, where E=Escalation, S=Stay, D=De-escalation and DU=Elimination due to unacceptable toxicity. The format of this matrix follows Ji et al [2010].[1]

For Arms A and B, the MTD estimate will be selected using the approach of the general interval design with the additional requirement that the isotonic estimate of DLT rate for the estimated MTD must be less than or equal to 32%.

Modified Toxicity Probability Interval (mTPI) Method

As the mTPI method is used for $2 \le n_j \le 4$, a brief description of the method based on its own framework[1] is provided here.

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 0.25 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 [0.20, 0.32]. 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.

The MTD estimation at the end of the trial for the general interval design is the same as the approach of the mTPI method.

Simulations for Interval Design Implemented for Arms A and B

The interval design as implemented for Arms A and B were examined via simulations. For each simulation, a sample size of 40 is used with a cohort size of 3 patients. Five scenarios were simulated with 10,000 simulations each. The simulation results are summarized in the table that follows. The frequency of the true MTD being selected if all 40 patients are enrolled by the interval design ranges from 58% to 89%, which are deemed satisfactory. The frequency of the true MTD being selected if 30 patients are enrolled is 53% to 81% (results not shown).

	Dose Level							
	1#	2	3	4	5	6	7	8
Scenario 1								
True DLT rate	0.02	0.05	0.25	0.50	0.6	0.7	0.8	0.9
Mean number of patients treated	3.3528	9.4656	20.3553	8.1030	0.6816	0.0393	0.0024	0.0
Mean number of patients with DLTs	0.0673	0.4718	5.0665	4.0585	0.4057	0.0273	0.002	0.0
Frequency selected as MTD	0.0000	0.0509	0.8904	0.0576	0.0011	0.000	0.00	0.00
Scenario 2								
True DLT rate	0.02	0.05	0.10	0.25	0.5	0.6	0.7	0.8
Mean number of patients treated	3.3366	4.3722	10.2312	16.6578	6.7098	0.6471	0.0447	0.00
Mean number of patients with DLTs	0.0668	0.2233	1.0247	4.2012	3.3318	0.3918	0.0310	0.00
Frequency selected as MTD	0.00	0.0021	0.1615	0.7629	0.0709	0.0026	0.00	0.00
Scenario 3								
True DLT rate	0.02	0.05	0.10	0.10	0.25	0.5	0.6	0.7
Mean number of patients treated	3.3369	4.2357	5.4972	8.9586	13.7136	5.6715	0.5508	0.0357
Mean number of patients with DLTs	0.0693	0.2103	0.5526	0.8970	3.4233	2.8307	0.3328	0.252
Frequency selected as MTD	0.0000	0.0008	0.0276	0.1768	0.7164	0.0754	0.0028	0.0002
Scenario 4								
True DLT rate	0.01	0.02	0.05	0.05	0.05	0.10	0.25	.50
Mean number of patients treated	3.120	3.3474	3.7638	3.7803	4.2186	7.9455	10.9323	4.8906
Mean number of patients with DLTs	0.0307	0.0714	0.1851	0.1882	0.2180	0.7812	2.7434	2.4528
Frequency selected as MTD	0.0000	0.0000	0.0014	0.0031	0.0109	0.2053	0.7106	0.0683
Scenario 5								
True DLT rate	0.0000	0.0000	0.000	0.0100	0.0200	0.0500	0.1500	0.2500

Mean number of patients treated	3	3	3.0039	3.1164	3.3408	5.0304	8.9601	12.3021
Mean number of patients with DLTs	0.0000	0.0000	0.0000	0.0000	0.00686	0.2563	1.3543	3.0638
Frequency selected as MTD	0.0000	0.000	0.000	0.000	0.0002	0.0181	0.3652	0.5810

starting dose.

Appendix 2.2. Definition of Progression-Free Survival (Expansion only)

PFS (Primary Definition – Specific to This Study): Requires Objective Progression Documentation

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	Start Date	Censored
No on-study assessments	Start Date	Censored
Alive, not started new anti-cancer treatment and no progression	Date of last objective tumor assessment documenting no progression	Censored
Progression documented on or between scheduled tumor assessments	Date of first objective tumor assessment documenting objective progression	Progressed (Event)
New anticancer treatment after discontinuation of treatment without progression	Date of last objective tumor assessment documenting no progression prior to new anticancer treatment	Censored
Death prior to 13 weeks since start date	Date of death	Death (Event)
Death without objective progression	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments (>13 weeks since last tumor assessment within the first 12 cycles or > 19 weeks from cycle 13 on)	Date of last objective tumor assessment documenting no progression prior to the event	Censored

1: For date of censorship, if a tumor assessment takes place over a number of days (eg, superficial lesions one day, scans another), the last date is used as the assessment date.