A PHASE 1 DOSE ESCALATION STUDY EVALUATING THE SAFETY AND TOLERABILITY OF PF-06804103 IN PATIENTS WITH HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) POSITIVE AND NEGATIVE SOLID TUMORS

Investigational Product Number:	PF-06804103
Investigational Product Name:	Not applicable
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	2017-002538-22
Protocol Number:	C0541001
Phase:	Phase 1

Document History

Document	Version Date	Summary of Changes and Rationale
Protocol Amendment 4	24 January 2020	The changes in Amendment 4 include: Introduction, Background, and Rationale: • Numerous changes were made to the headings and content of these sections to streamline previous text, and to revise or add new information relevant to the study design changes. Protocol Summary • Revised as appropriate for consistency with the body of the document. Schedule of Activities • Main and PK tables were divided to more clearly reflect monotherapy dosing and sample collection activities and combination therapy dosing and sample collection activities. • Individual changes were made to each table to remove or add activities required for each study part. o Footnotes were updated as appropriate to reflect the design changes. [redacted] Study Objectives and Endpoints • clarified and revised to reflect the changes to the study design . Study Design and Schematic

		• Schematic revised to reflect new study design. • Updated or added language for each study part to reflect the changes to the study populations, the dose levels to be explored, the number of patients to be evaluated, the criteria for dose escalation, and the dose expansion plan for monotherapy and combination therapy. Dose Limiting Toxicity • Revised to include DLT information for newly defined treatment arms. Inclusion/Exclusion Criteria • Headings for General Inclusion and General Exclusion were added as well as subheadings for treatment arms with specific requirements. • Revised to remove the GC and NSCLC arms after Part 1A • Updated to be more specific for each of the patient populations to be evaluated in the rest of the study including: o In Part 1B, postmenopausal patients with HR-positive HER2 IHC 1+ or IHC 2+/ISH- BC o In Part 2A, HER2-positive BC patients in 3L o In Part 2B, patients with HR-positive HER2 IHC 1+ or IHC 2+/ISH- BC in the 1L Study Treatments • Revised to include a description of study treatments by study part and clarify that all study treatment are considered

		investigational products • Remove "/kg" from Table 8 in reference to palbociclib dose Allocation to Treatment Procedures: • updated to reflect the potential use of IRT/and IWR Patient Compliance • Updated to reflect compliance tracking method for IP administration for each study part Investigational Product Supplies (Form and Packaging) • Added dosing form and packaging information added for each IP Administration of Investigational Products: • Added administration of IP details for each IP • Updated premedication instructions and process information for handling infusion-related reactions Dose Delays • Section revised to clarify processes for Q2W and Q3W dosing schedules. Dose Modifications • Dose modification information added for each IP to be administered as monotherapy and in combination therapy. • Dose modification tables for each IP added to appendices. Re-Treatment Criteria

		• Section added to clarify retreatment procedures. Concomitant medications • Concomitant medication information added for palbociclib. Patient Withdrawal • Updates to language to ensure proper documentation is recorded in the medical records and database Diffusing Capacity of the Lungs for Carbon Dioxide • Revised acceptable ranges. Tumor Biopsies • Section revised to differentiate Part 1 and Part 2 tumor collection requirements, optional biopsies, and biopsy samples collected for biomarker assessment. o Corresponding data added to footnotes of the SOA Analysis Sets • Section revised for clarity and conciseness, major treatment deviation criteria removed and cross reference added to appropriate section. Statistical Methods and Properties • Section revised to remove redundant table and MTD information, and revise sample size language. • Sample Size Determination Updated language to accommodate new design and new patient sample sizes

		Appendices: • Table describing HER2 IHC and/or ISH status descriptions added • Tables describing dose modification guidelines added Table of Drugs known to predispose patients the Torsade de Pointes added
Editorial, grammatical, and administrative changes were made throughout the document, including changes and additions to the List of Abbreviations.		
Protocol Amendment 3	25 April 2019	The changes in Amendment 3 include:
		• Schedule of Activities: • A notation was added that the visit window for a complete visit applies to all assessments on the study visit. • Additional guidance on the timing of diffusing capacity of the lungs for carbon monoxide (DLco) measurements for patients on study past 12 months is provided in footnote #10. • The tumor biopsy sampling (footnote 20) was re-written to split out and clarify biopsy collection based on each part and arm of the study and the patient population. These modifications are also reflected in Section 7.3.5. Tumor Biopsies. Rationale: To add clarity for visits and visit windows, clarify DLco assessments after 12 months on study and provide details for tumor biopsy collection requirements.
		• Schedule of Pharmacokinetic, Immunogenicity, and Biomarker/Pharmacodynamic Assessments:

		• Flexibility for the 1-hour sample time point was added and details were provided for post-dose PK sampling window periods. CCI [redacted] Rationale: To broaden the window period to reduce protocol deviations and add time points for collection of blood samples for CTCs.
		CCI [redacted] CCI [redacted]
		• The Study Overview section in the protocol summary and "Section 3.1. Study Overview" was updated to differentiate each HER2 status required by Arm for Part 2. Rationale: The required HER2 expression levels were added for each Part 2 Arm (patient population).
		• The Overall Study Design figure (Figure 1) was updated. Rationale: To align with "Section 3.1 Study Overview" and the updates to Section 4.1 and 4.2 Eligibility Criteria.
		• Table 1. for PF-06804103 Dose Escalation Levels was modified to reflect additional dose levels beyond 4.0 mg/kg based on the

		footnote that higher doses may be explored. Changes were also reflected in Table 6. in Section 9.2. Statistical Methods and Properties. Rationale – The study is enrolling at doses higher than 4 mg/kg and is supported by the footnote that higher doses may be explored.
		• Text was added to Section 3.4 Dose Expansion Phase (Part 2) to define the steps that will be taken once the MTD/RP2D has been determined in Part 1. Rationale: Direct the reader to the modified criteria in "Section 4.1. Inclusion Criteria" and Section 4.2. Exclusion Criteria" for Part 2.

		• "Section 4.1. Inclusion Criteria".
		
		  • Part 1 and Part 2 were modified to define the specific criteria for each part of the study and each study population.
		
		  • Patients are required to have access to archival tumor sample.
		
		Rationale: Part 1 was modified to provide additional clarity. Part 2 was modified to (1) define the biomarker driven population and (2) outline the specific lines of therapy for each patient population prior to study entry. In addition, all patients will be required to have access to archival tissue sample to be retrospectively assessed for HER2 expression. This was previously described in the Schedule of Activities footnote 20.

		• "Section 4.2. Exclusion Criteria": #7 was removed. The criteria previously excluded patients in Part 2 that received prior TDM-1. Rationale: To study a patient population who received all prior monoclonal HER2 targeted therapies.

		• Korea specific language was added to the document as required by regulatory agency feedback. Rationale: Previously addressed and agreed to in a protocol clarification letter.
		• "Section 5.4.3. Dose Reductions": Table 3 and Figure 2 were clarified for dose reduction criteria and algorithm for continuation and discontinuation of PF-06804103 based on LVEF assessments while on study. Rationale: The text was contradictory and required modification.
		• "Section 6.4.1. Request to Continue Treatment" was added to allow the investigator and Sponsor to discuss the option for a patient to remain on study if deriving clinical benefit.
		• A timeframe was added to "Section 7.1.5. (12 Lead) Electrocardiogram" for the 3 consecutive ECGs. Rationale: To allow flexibility when performing the ECGs. • "Section 7.1.7. Diffusing Capacity of the Lungs for Carbon Dioxide": The units for on study measuring of DLco assessments were added. Rationale: In order to grade DLco assessments by CTCAE, the unit of measurement required an update. This grading is necessary for the determination of potential Dose Reductions/Discontinuations (Table 3).
		• "Section 9. The Data Analysis/Statistical Methods" were updated to reflect the target patient population being studied. Rationale: To provide sufficient sample size to

		be able to draw preliminary assessment on safety and clinical activity.
Protocol Amendment 2	11 January 2018	The changes in Amendment 2 include: • Exclusion of patients with a history of prior malignancy other than the diseases under study within the past 5 years – Section 4.2. Rationale – Additional criteria included to address feedback from regulatory agency. • Requirement for use of effective contraception extended from 28 days to 90 days post the last dose of study treatment – Schedule of Activities and Sections 4.2, 4.3 and 7.1.1. Rationale – Requirement revised to address feedback from regulatory agency. • Requirement for a minimum 48-hour interval between dosing of new patients during the dose escalation portion of the study – Section 3.1.1. Rationale – Requirement added to address feedback from regulatory agency. • Administrative changes – Schedule of Activities, Sections 3.1, 4.1 and 9.3. Rationale – Administrative changes and corrections.
Protocol Amendment 1	06 September 2017	The changes in Amendment 1 include: • Revisions to the dose limiting toxicity criteria definition – Section 3.2. Rationale – Additional criteria included, and existing criteria revised to address feedback from regulatory agency. • Modifications to inclusion criteria 1 and 2 to further define the relevant patient

		populations – Section 4.1. Rationale – Addition of reference to the specific criteria to be used to address feedback from regulatory agency as well as simplification of the criteria for Part 2. • Inclusion of prior therapies required for non-small cell lung cancer patients added to inclusion criteria 3 – Section 4.1. Rationale – Revised to address feedback from regulatory agency. • Revisions to timing for pregnancy tests prior to receipt of the first study treatment – Schedule of Activities and Section 7.1.1. Rationale – Revision to timing for second negative pregnancy test given the study will enroll patients requiring expedited treatment for their life-threatening condition. • Removal of blood sample for surfactant protein-A (SP-A) and SP-D test – Schedule of Activities and Section 7.1.7. Rationale – High resolution imaging as well as diffusing capacity of the lungs for carbon monoxide determined to be sufficient assessments for monitoring of potential pulmonary toxicity. • Inclusion of amylase and lipase as required blood chemistry assessment evaluations – Schedule of Activities and Section 7.1.3. Rationale – Analytes added to ensure appropriate monitoring for new dose limiting toxicity criteria. • Decrease in frequency of echocardiogram/multigated acquisition scan evaluation after one year of study treatment. – Schedule of Activities. Rationale – Frequency of assessments

		decreased to reduce the number of assessments after sufficient safety monitoring period has been completed. [redacted] • Revision to definition for inclusion of patients in the DLT observation who discontinue study close to Day 21 – Section 3.1.1. Rationale – Editorial clarification. • Revision to exclusion criteria for carbon monoxide diffusing capacity – Section 4.2. Rationale – Editorial clarification. • Administrative and editorial revisions – Schedule of Activities, Section 3.1, 3.1.1, 3.3, 4.2, 5.1, 5.4, 5.4.2, 7.1.4, 7.2.1, 7.3.3 and Table 3.
Original protocol	15 May 2017	Not applicable (N/A)

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

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PROTOCOL SUMMARY

Background and Rationale

HER2 is a receptor tyrosine kinase that is involved in the regulation of various cellular functions. Aberrant HER2 receptor activation has been implicated as a driving factor in the tumorigenesis and progression of a number of cancers.[34,27,23]

To date, 3 HER2-specific monoclonal antibodies have been approved by regulatory agencies for treating HER2-positive metastatic breast cancer: trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1). Although these HER2-targeting therapies have transformed the clinical practice for HER2-positive breast cancer and have resulted in survival benefits, not all patients respond to the therapies. The vast majority of patients who initially respond to the treatment will eventually relapse. This is thought to be due to the high degree of intratumoral heterogeneity of HER2 expression in breast cancer and lack of efficacy of current anti-HER2 therapeutics in tumor cells expressing relatively low levels of HER2. A great deal of effort has been put into developing better anti-HER2 agents that can kill cancer cell populations expressing a broad range of HER2.[15,19] Given the lack of clinical success in developing therapies to treat tumors with relatively low levels of HER2, this remains an area of high unmet medical need.

The frequency of HER2 overexpression in GC ranges from 4.4% to 53.4%, with a mean of 17.9%.[3,25,33,8,11,6,16,4,7,14,20,30,2,13] Similar to breast cancer, HER2-positive status in gastric cancer was associated with decreased survival and clinicopathological features of tumor progression, such as serosal invasion, metastases and higher disease stage.[13] The results clearly set HER2 as a negative prognostic factor, suggesting that HER2 overexpression/amplification is a molecular abnormality that might be associated with the development of gastric cancer.[16,13] To date, one HER2-specific monoclonal antibody has been approved by regulatory agencies for treating HER2-positive gastric cancer: trastuzumab. However, that approval was for combination therapy with cisplatin and a fluoropyrimidine (chemotherapy) and there was only an increase in median survival of 2 months over chemotherapy alone.

Although HER2 overexpression has been reported in 13% to 20% of NSCLC, 3+ expression is observed only in 2% to 6%.[10,9,36] FISH assessed *HER2* gene amplification is unusual, and it has been reported in 2% to 4% of NSCLCs, mainly of adenocarcinoma-type. Comparably to breast cancer, in spite of the lack of large series, concordance between FISH and immunohistochemistry (IHC) 3+ has been confirmed.[9] In our internal IHC analysis of 24 NSCLC specimens, 6 showed 2+/3+ HER2 expression.

ADCs are a class of drugs that use antibodies specifically targeting tumor-associated antigens as vehicles to deliver covalently attached small-molecule toxins into cancer cells.[24] PF-06804103 is an anti-human epidermal growth factor receptor 2 (HER2) ADC that is currently being investigated in patients with HER2 positive solid tumors.

Significant tumor growth control has been observed in preclinical tumor models for various indications, including BC AND GC with HER2 IHC 1+ and IHC2+ levels of HER2

expression. This suggests that PF-06804103 may have the potential to provide therapeutic benefit to patients currently ineligible for HER2 targeted therapy.

In an effort to identify patients with lower levels of HER2 protein who may respond to PF-06804103, patients with tumors expressing HER2 IHC 1+ and HER IHC 2+/ISH- will be included and patients with HER2 IHC 0 tumors will continue to be excluded from this study.

This study will be conducted in 2 parts, dose escalation and dose expansion. PF-06804103 will be administered as monotherapy in escalating doses, and then as part of a combination regimen with palbociclib and letrozole. For part 2 combination therapy, patients with HR-positive, HER2 IHC 1+ or IHC 2+/ISH- BC will receive PF-6804103 (an anti HER2-ADC consisting of an auristatin anti-microtubulin inhibitor payload site-specifically conjugated onto a Herceptin molecule using a cleavable linker), as combination therapy with an aromatase inhibitor (letrozole) and a CDK4/6 inhibitor (palbociclib) as 1L treatment.

Study Objectives and Endpoints

Objective:	Endpoint:
Primary	
To characterize the DLTs of escalating levels of PF-06804103 To assess the safety and tolerability of PF-06804103 To determine the RP2D for PF-06804103 as monotherapy To determine the RP2D for PF-06804103 in combination with palbociclib and letrozole	First cycle (21 days) DLTs – Part 1A First cycle (28 days) DLTs – Part 1B All available safety data including: AEs, SAEs, and clinically meaningful abnormalities in laboratory values and vital signs
Part 2: To investigate preliminary antitumor activity	Part 2 y: OR, as assessed using RECIST version 1.1. Time-to-event endpoints: DR, PFS, TTP
Secondary	
Objective	**Endpoint**
To characterize the single and multiple dose PK of PF-06804103 ADC, total antibody and unconjugated payload (PF-06380101).	SD and MD PK parameters of PF-06804103 ADC, total antibody and unconjugated payload (PF-06380101).
To evaluate the immunogenicity of PF-06804103	Incidence and titers of ADA and NAbs against PF-06804103
To document antitumor activity	OR, as assessed using RECIST version 1.1. Time-to-event endpoints: DR, PFS, TTP – Part 1
To explore preliminary antitumor activity in patients that HER2 positive GC	HER2 expression levels in pre-treatment tumor biopsies via IHC and ISH

Study Design

This is a Phase 1, open-label, multicenter, multiple dose, safety, PK, and PD study of PF-06804103 in adult patients with HER2-positive solid tumors (BC and GC [Part 1A only]) and in postmenopausal patients with HR-positive HER2 IHC 1 + or IHC 2+/ISH- BC. Part

1A and 1B will evaluate escalating doses of PF-06804103 as monotherapy and as part of a combination regimen, respectively. Part 2A and Part 2B will evaluate selected doses of PF-06804103 in expansion cohorts as monotherapy and in a combination regimen, respectively.

Approximately 148 patients are expected to be enrolled in the study overall. The actual number of patients enrolled will depend on the tolerability of PF-06804103 and the number of dose levels required to identify the MTD and select dose levels for Part 2 of the study.

Study Treatments

In Part 1A, PF-06804103 will be administered as an IV infusion every 21 days at a starting dose of 0.15 mg/kg, dose escalation is planned as described in Table 5. Treatment with investigational products will continue until either disease progression, patient refusal, or unacceptable toxicity occurs, whichever occurs first, unless the investigator and medical monitor agree to treatment beyond progression based on individual benefit/risk assessments.

A modified toxicity probability interval (mTPI) method targeting a DLT rate of approximately 27.5% with an equivalence interval of (22.5%, 32.5%) will be utilized.

In Part 1B, dose escalation in the combination regimen will also follow the mTPI design. PF-06804103 will be administered as an IV infusion every 14 days in combination with SOC oral palbociclib and oral letrozole. Dose escalation or de-escalation (Table 7) will be based on all available clinical, safety, PK, and/or PD data.

The combination regimen evaluated in Part 1B will be administered to patients with 1L BC HR-positive/HER2 IHC 1 + or IHC 2+/ISH-.

The actual number of patients enrolled will depend on the tolerability of PF-06804103 at each of dose level when administered in combination with palbociclib and letrozole.

In Part 2A, PF-06804103 will be evaluated as monotherapy when administered as described below:

- Arm M1: ≥3L BC HER2-positive (HER2 IHC 3+ or ISH+) 3 mg/kg Q3W
- Arm M2: ≥3L BC HER2-positive (HER2 IHC 3+ or ISH+) 4. mg/kg Q3W
- Arm M3: ≥2L BC, HR-positive, HER2-negative (HER2 IHC 1+ or IHC 2+/ISH-) 4 mg/kg Q3W

In Part 2B, the PF-06804103 dose level will be selected based on the dose level determined in Part 1B and all available clinical, safety, preliminary efficacy, PK, and PD data. PF-06804103 will be administered in combination with palbociclib and letrozole to the patients described below:

- Arm C1: BC 1L, postmenopausal, HR-positive, HER2 IHC 1+ or IHC 2+/ISH-, PF-06804103 Q2W with SOC regimen for palbociclib and letrozole.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to Section 7 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 in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. Monotherapy Dose Escalation and Expansion – Schedule of Activities

Q3W Dosing		**Cycle 1** (Days 1-21)				**Cycles 2 and 3** (Days 1-21)			**Cycle 4** (Days 1 -21)				**Cycles 5 and Subsequent Cycles** (Days 1-21)			**Post Treatment**	
	Screen/Baseline (≤28 days)	**Day 1**	**Day 4 (Part 1A only)**	**Day 8 Part 1A only)**	**Day 15**	**Day 1**	**Day 8 (Part 1A only)**	**Day 15**	**Day 1**	**Day 4 (Part 1A only)**	**Day 8 (Part 1A only)**	**Day 15**	**Day 1**	**Day 8[24] (Part 1A only)**	**Day 15[24]**	**EOT[25]**	**Follow-Up[26]**
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	
Informed consent[1]	X																
Tumor history[2]	X																
Medical history[3]	X																
Complete PE	X	X[4]														X	
Symptoms directed PE				X	X	X	X	X	X		X	X	X	X	X		
Height	X																
Weight	X					X			X				X			X	
Vital signs[5]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Performance status[6]	X	X				X			X				X			X	X
12-Lead ECG[7]	X	X		X		X	X		X		X		X	X		X	
ECHO or MUGA[8]	X					Day 1 of Cycle 3, Cycle 6 and then Day 1 every 3 cycles thereafter										X	
DLco[9]	X					To be performed every 6 weeks starting at Cycle 3											
Contraception check	X	X				X			X				X			X	X
Ophthalmic Examination[10]	X																
Laboratory																	
Unique Screening Laboratory tests[11]	X																
Hematology[12]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	
Blood Chemistry[13]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	
Coagulation[14]	X					X			X				X			X	

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	Screen/Baseline (≤28 days)	**Day 1**	**Day 4 (Part 1A only)**	**Day 8 Part 1A only)**	**Day 15**	**Day 1**	**Day 8 (Part 1A only)**	**Day 15**	**Day 1**	**Day 4 (Part 1A only)**	**Day 8 (Part 1A only)**	**Day 15**	**Day 1**	**Day 8[24] (Part 1A only)**	**Day 15[24]**	**EOT[25]**	**Follow-Up[26]**
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	
Urinalysis[15] (Part 1A only)	X				X	X			X				X			X	
Pregnancy test[16]	X	X				X			X				X			X	X
Registration and Treatment																	
Registration[17]		X															
PF-06804103[18]		X				X			X				X				
Tumor assessments																	
CT or MRI scan or equivalent[19]	X	To be obtained every 6 weeks starting at Cycle 3														X[19]	
Other samplings																	
Tumor Tissue Samples[20]	X					X (Cycle 3 only)											
CCI																	
PK Blood Samples		Table 3. Pharmacokinetic, Immunogenicity, and Biomarker/Pharmacodynamic Assessments – Monotherapy Dosing															
Blood sample for Immunogenicity Test		Table 3. Pharmacokinetic, Immunogenicity, and Biomarker/Pharmacodynamic Assessments – Monotherapy Dosing															
Blood biomarker samples		Table 3. Pharmacokinetic, Immunogenicity, and Biomarker/Pharmacodynamic Assessments – Monotherapy Dosing															
Other clinical assessments																	
AE and SAE monitoring[22]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant treatment monitoring		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

*Unless otherwise stated below, the window period applies to all assessments on a given study visit.

1. May be collected more than 28 days prior to study entry.
2. Includes details of primary diagnosis and treatment history.
3. Includes medical history of disease process other than the cancer under study (active or resolved) and significant concurrent illness. Includes prior

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Q3W Dosing		Cycle 1 (Days 1-21)				Cycles 2 and 3 (Days 1-21)			Cycle 4 (Days 1 -21)				Cycles 5 and Subsequent Cycles (Days 1-21)			Post Treatment	
	Screen/Baseline (≤28 days)	Day 1	Day 4 (Part 1A only)	Day 8 Part 1A only)	Day 15	Day 1	Day 8 (Part 1A only)	Day 15	Day 1	Day 4 (Part 1A only)	Day 8 (Part 1A only)	Day 15	Day 1	Day 8[24] (Part 1A only)	Day 15[24]	EOT[25]	Follow-Up[26]
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	

treatments and any current medical treatment for any condition.

4. No need to repeat on C1D1 if baseline assessment is performed within 3 days of dosing.
5. Includes temperature, BP, and pulse rate (to be recorded in a supine or seated position), and pulse oximetry. On Day 1 of each 21 day cycle, vital signs should be measured prior to infusion start (pre-dose) and BP and PR will be repeated 1 hour after the start of the infusion (ie, just prior to the end of the infusion).
6. ECOG – see Appendix 2.
7. Triplicate ECGs will be collected during Screening and at the End of Treatment. Additional ECGs will be collected prior to dosing and at the end of infusion on dosing days as well as on Day 8. When ECGs coincide with PK sampling, the ECG should be recorded before PK samples are drawn, so that the PK sample is collected at the nominal time. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs should be performed if clinically indicated (Section 7.1.5).
8. To be conducted at screening, Cycle 3, Cycle 6 and then every 3 cycles thereafter through the first year of study treatment. The frequency will change to every 6 months after one year of study treatment, unless clinically indicated. If LVEF is reported as a range, the average should be reported. ECHO or MUGA scans should also be performed in the case of an adverse event which may be related to cardiac dysfunction in the opinion of the investigator. The same modality used during screening should preferably be used for all subsequent timepoints.
9. To be conducted at screening, Cycle 3 and then every other cycle at the same timepoints when imaging tumor assessments are performed. If the tumor assessment frequency is reduced to every 12 weeks after 6 months (±7 days) of study treatment (see footnote 19 below), the Dlco assessment should remain on a schedule of every 4th cycle. (Section 7.1.7).
10. An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes BCVA, IOP preferably by Goldmann applanation, biomicroscopic examination to evaluate the lids/lashes/adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and dilated fundus exam to evaluate the optic nerve, vessels, macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow-up.
11. HBV, hepatitis B core antibody, HCV and HIV as well as FSH and estradiol for post-menopausal women who are amenorrhoeic for at least 12 consecutive months only. Samples will be analyzed locally.
12. CBC to include hemoglobin, platelets, WBC, absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils. No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing. Samples will be analyzed locally.
13. Should include ALT, AST, ALP, sodium, potassium, magnesium, chloride, total calcium, total bilirubin, BUN or urea, creatinine, uric acid, glucose

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Q3W Dosing		Cycle 1 (Days 1-21)				Cycles 2 and 3 (Days 1-21)			Cycle 4 (Days 1 -21)				Cycles 5 and Subsequent Cycles (Days 1-21)			Post Treatment	
	Screen/Baseline (≤28 days)	Day 1	Day 4 (Part 1A only)	Day 8 Part 1A only)	Day 15	Day 1	Day 8 (Part 1A only)	Day 15	Day 1	Day 4 (Part 1A only)	Day 8 (Part 1A only)	Day 15	Day 1	Day 8[24] (Part 1A only)	Day 15[24]	EOT[25]	Follow-Up[26]
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	

(non-fasted), bicarbonate or CO_2, albumin, phosphorus or phosphate, amylase and lipase. No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing.

14. Should include INR or PT.
15. Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Abnormal test results will be managed as indicated.
16. For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study treatment – once at the start of screening and once immediately before the first investigational product administration. Pregnancy tests will also be routinely repeated at every cycle (21 days) during the active treatment period, at the EOT and Follow-up visits and whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by the IRB or IECs or if required by local regulations.
17. Patient number and dose level allocation assigned by Pfizer Inc. Registration should occur before any other Day 1 activities are performed.
18. Will be administered once every 21 days as an IV infusion over approximately 60 minutes (±15 minutes).
19. Tumor assessments will include all known or suspected disease sites and may include chest, abdomen and pelvis CT or MRI scans. Brain scans and bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. At minimum, the chest CT must be a high-resolution scan with a 1 mm slice thickness. Baseline CNS MRI is not required with the exception of symptomatic patients to rule out CNS metastases (CT is an option if MRI is not available or tolerated by the patient). CT or MRI scans are to be done every 6 weeks (±7 days) from the start of study treatment until disease progression by RECIST (v1.1) or death, or until permanent discontinuation of study treatment. The frequency will be reduced to every 12 weeks after 6 months (±7 days) of study treatment. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Tumor assessments should be repeated at the EOT visit if more than 6 weeks have passed since the last evaluation.
20. Patient enrollment will be based on prior testing for HER2 positivity by an FDA approved, or locally validated, diagnostic test. **Part 1A:** Fresh pre-treatment (screening) and Day 1 Cycle 3 (±5 days) biopsy collections are optional. Archival tissue from a prior biopsy will be collected **from all patients** for central evaluation if available. If collected, the pre-treatment biopsy should be completed after all eligibility criteria have been verified and should be taken from the same lesion, not previously irradiated, if possible. If the patient discontinues the study before Cycle 3, Day 1 the patient will be asked to provide a fresh biopsy at the EOT visit. Bone biopsies, cytological specimens and fine-needle aspiration samples are excluded (Section 7.4.5). **Part 2:** A mandatory fresh pre-treatment, diagnostic quality biopsy, representative of the diagnosed malignancy, will be collected at screening from all patients CCI [redacted] to retrospectively confirm HER2 expression. An archival sample collected prior to study start may be substituted for the mandatory pre-treatment biopsy if no prior anti-HER2 treatment between the collection of this tumor sample and study start had been administered. In

Table 1. Monotherapy Dose Escalation and Expansion – Schedule of Activities

Q3W Dosing		Cycle 1 (Days 1-21)				Cycles 2 and 3 (Days 1-21)			Cycle 4 (Days 1 -21)				Cycles 5 and Subsequent Cycles (Days 1-21)			Post Treatment	
	Screen/Baseline (≤28 days)	Day 1	Day 4 (Part 1A only)	Day 8 Part 1A only)	Day 15	Day 1	Day 8 (Part 1A only)	Day 15	Day 1	Day 4 (Part 1A only)	Day 8 (Part 1A only)	Day 15	Day 1	Day 8[24] (Part 1A only)	Day 15[24]	EOT[25]	Follow-Up[26]
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	

additioan, for up to 10 patients in each arm, a mandatory fresh on-treatment diagnostic quality biopsy, representative of the diagnosed malignancy, will be collected at Day 1 Cycle 3 (±5 days). If the patient discontinues the study before the scheduled on-treatment biopsy, the patient will be asked to provide a fresh biopsy at the EOT visit. Bone biopsies, cytological specimens and fine-needle aspiration samples are excluded (Section 7.4.5).

CCI [redacted]

22. AEs should be documented and recorded at each visit using the NCI CTCAE version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
23. All concomitant medications and non-drug supportive interventions should be recorded on the CRF.
24. Beginning at Cycle 6, the Day 8 and Day 15 visits are no longer required.
25. Perform if not completed in the last week (last 6 weeks for tumor assessments).
26. At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, 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.

Table 2. Combination Regimen Escalation and Expansion – Schedule of Activities

Q2W Dosing		**Cycle 1** (Days 1-28)				**Cycles 2 and 3** (Days 1-28)			**Cycle 4** (Days 1 -28)				**Cycles 5 and Subsequent Cycles** (Days 1-28)			**Post Treatment**	
	Screen/Baseline (≤28 days)	**Day 1**	**Day 4**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 4**	**Day 8**	**Day 15**	**Day 1**	**Day 8[25]**	**Day 15**	**EOT[26]**	**Follow-Up[27]**
Visit Window (days)*			**(±1)**	**(±1)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(±1)**	**(±1)**	**(±2)**	**(±2)**	**(±2)**	**(±2)**	**(+7)**	**(+7)**
Protocol Activity																	
Informed consent[1]	X																
Tumor history[2]	X																
Medical history[3]	X																
Complete PE	X	X[4]														X	
Symptoms directed PE				X	X	X	X	X	X		X	X	X	X	X		
Height	X																
Weight	X					X			X				X			X	
Vital signs[5]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Performance status[6]	X	X				X			X				X			X	X
12-Lead ECG[7]	X	X		X		X	X		X		X		X	X		X	
ECHO or MUGA[8]	X					Day 1 of Cycle 3, Cycle 6, and then Day 1 every 3 cycles thereafter										X	
Dlco[9]	X					To be performed every 8 weeks starting at Cycle 3											
Contraception check	X	X				X			X				X			X	X
Ophthalmic Examination[10]	X																
Laboratory																	
Unique screening laboratory tests[11]	X																
Hematology[12]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	
Blood Chemistry[13]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	
Coagulation[14]	X					X			X				X			X	
Pregnancy test[15]	X	X				X			X				X			X	X
Registration and Treatment																	
Registration[16]		X															
PF-06804103[17]		X			X	X		X	X			X	X		X		
Palbociclib[18]		once daily on Days 1 through 21 of each cycle followed by a 7-day rest period															
Letrozole[19]		once daily															
Tumor assessments																	

Table 2. Combination Regimen Escalation and Expansion – Schedule of Activities

Q2W Dosing		Cycle 1 (Days 1-28)				Cycles 2 and 3 (Days 1-28)			Cycle 4 (Days 1 -28)				Cycles 5 and Subsequent Cycles (Days 1-28)			Post Treatment	
	Screen/Baseline (≤28 days)	Day 1	Day 4	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 4	Day 8	Day 15	Day 1	Day 8[25]	Day 15	EOT[26]	Follow-Up[27]
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	
CT or MRI scan or equivalent[20]	X					To be obtained every 8 weeks starting at Cycle 3										X[19]	
Other samplings																	
Tumor Tissue Samples[21]	X					X (Cycle 3 only)											
CCI																	
PK Blood Sampling		Table 4. Pharmacokinetic, Immunogenicity, and Biomarker/Pharmacodynamic Assessments – Combination Regimen (PF 6804103 in combination with Palbociclib and Letrozole)															
Blood sample for Immunogenicity Test		Table 4. Pharmacokinetic, Immunogenicity, and Biomarker/Pharmacodynamic Assessments – Combination Regimen (PF 6804103 in combination with Palbociclib and Letrozole)															
Blood biomarker samples		Table 4. Pharmacokinetic, Immunogenicity, and Biomarker/Pharmacodynamic Assessments – Combination Regimen (PF 6804103 in combination with Palbociclib and Letrozole)															
Other clinical assessments																	
AE and SAE monitoring[23]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant treatment(s)[24]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

*Unless otherwise stated below, the window period applies to all assessments on a given study visit.

1. May be collected more than 28 days prior to study entry.
2. Includes details of primary diagnosis and treatment history.
3. Includes medical history of disease process other than the cancer under study (active or resolved) and significant concurrent illness. Includes prior treatments and any current medical treatment for any condition.
4. No need to repeat on C1D1 if baseline assessment is performed within 3 days of dosing.
5. Includes temperature, BP, and pulse rate to be recorded (in a supine or seated position) and pulse oximetry. On Day 1 of each 28 day cycle, vital signs should be measured prior to infusion start (pre-dose) and BP and PR will be repeated 1 hour after the start of the infusion (ie, just prior to the end of the infusion).
6. ECOG – see Appendix 2.
7. Triplicate ECGs will be collected during Screening and at the End of Treatment. Additional ECGs will be collected prior to dosing and at the end of infusion on dosing days as well as on Day 8. When ECGs coincide with PK sampling, the ECG should be recorded before PK samples are drawn so that

Table 2. Combination Regimen Escalation and Expansion – Schedule of Activities

Q2W Dosing		Cycle 1 (Days 1-28)				Cycles 2 and 3 (Days 1-28)			Cycle 4 (Days 1 -28)				Cycles 5 and Subsequent Cycles (Days 1-28)			Post Treatment	
	Screen/Baseline (≤28 days)	Day 1	Day 4	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 4	Day 8	Day 15	Day 1	Day 8[25]	Day 15	EOT[26]	Follow-Up[27]
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	

the PK sample is collected at the nominal time. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs should be performed if clinically indicated (Section 7.1.5).

8. To be conducted at screening, Cycle 3, Cycle 6 and then every 3 cycles thereafter through the first year of study treatment. The frequency will change to every 6 months after one year of study treatment, unless clinically indicated. If LVEF is reported as a range, the average should be reported. ECHO or MUGA scans should also be performed in the case of an AE which may be related to cardiac dysfunction in the opinion of the investigator. The same modality used during screening should preferably be used for all subsequent timepoints.
9. To be conducted at screening, Cycle 3 and then every other cycle at the same timepoints when imaging tumor assessments are performed. If the tumor assessment frequency is reduced to every 12 weeks after 6 months (±7 days) of study treatment (see footnote 20 below), the Dlco assessment should remain on a schedule of every 4th cycle. (Section 7.1.7).
10. An eye exam (performed by an ophthalmologist) will be performed at screening. The eye exam includes BCVA, IOP preferably by Goldmann applanation, biomicroscopic examination to evaluate the lids/lashes/adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and dilated fundus exam to evaluate the optic nerve, vessels, macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow-up.
11. HBV, hepatitis B core antibody, HCV, and HIV as well as FSH and estradiol for post-menopausal women who are amenorrhoeic for at least 12 consecutive months only. Samples will be analyzed locally.
12. CBC to include hemoglobin, platelets, WBC, absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils. No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing. Samples will be analyzed locally.
13. Should include ALT, AST, ALP, sodium, potassium, magnesium, chloride, total calcium, total bilirubin, BUN or urea, creatinine, uric acid, glucose (non-fasted), bicarbonate or CO_2, albumin, phosphorus or phosphate, amylase and lipase. No need to repeat on C1D1 if baseline assessment performed within 3 days of dosing.
14. Should include INR or PT.
15. For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study treatment – once at the start of screening and once immediately before the first investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the EOT and Follow-up visits and whenever 1 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.
16. Patient number and dose level allocation assigned by Pfizer Inc. Registration should occur before any other Day 1 activities are performed.
17. Will be administered once every 14 days as an IV infusion over approximately 60 minutes (±15 minutes).

Table 2. Combination Regimen Escalation and Expansion – Schedule of Activities

Q2W Dosing		Cycle 1 (Days 1-28)				Cycles 2 and 3 (Days 1-28)			Cycle 4 (Days 1 -28)				Cycles 5 and Subsequent Cycles (Days 1-28)			Post Treatment	
	Screen/Baseline (≤28 days)	Day 1	Day 4	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 4	Day 8	Day 15	Day 1	Day 8[25]	Day 15	EOT[26]	Follow-Up[27]
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	

18. Palbociclib: Patients will self-administer palbociclib (125 mg) PO QD (Day 1 through 21), followed by 1 week off, and repeat every 28 days. Patients will record each dose in their patient diary.
19. Letrozole: Patients will self-administer daily (2.5 mg) PO QD (Days 1 through 28). Patients will record each dose in their patient diary.
20. Tumor assessments will include all known or suspected disease sites and may include chest, abdomen and pelvis CT or MRI scans. Brain scans and bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. At minimum, the chest CT must be a high-resolution scan with a 1 mm slice thickness. Baseline CNS MRI is not required with the exception of symptomatic patients to rule out CNS metastases. (CT is an option if MRI is not available or tolerated by the patient). CT or MRI scans are to be done every 8 weeks (±7 days) from the start of study treatment until disease progression by RECIST (v1.1) or death, or until permanent discontinuation of study treatment. The frequency will be reduced to every 12 weeks after 6 months (±7 days) of study treatment unless more frequent scans are clinically indicated. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Tumor assessments should be repeated at the EOT visit if more than 6 weeks have passed since the last evaluation.
21. **Part 1B:** Fresh pre-treatment (screening) and Day 1 Cycle 3 (±5 days) biopsy collections are optional. Archival tissue from a prior biopsy will be collected from all patients for central evaluation if available. If collected, the pre-treatment biopsy should be completed after all eligibility criteria have been verified and should be taken from the same lesion, not previously irradiated, if possible. If the patient discontinues the study before Cycle 3, Day 1 the patient will be asked to provide a fresh biopsy at the EOT visit. Bone biopsies, cytological specimens and fine-needle aspiration samples are excluded (Section 7.4.5).
Part 2: A mandatory fresh pre-treatment, diagnostic quality biopsy, representative of the diagnosed malignancy, will be collected at screening from all patients CCI [redacted] to retrospectively confirm HER2 expression. An archival sample collected prior to study start may be substituted for the mandatory pre-treatment biopsy if no prior anti-HER2 treatment between the collection of this tumor sample and study start had been administered. If the patient discontinues the study before the scheduled on-treatment optional biopsy, the patient will be asked to provide a fresh biopsy at the EOT visit. The EOT optional biopsy will be requested of patients who discontinue prior to Cycle 3 Day 1. Bone biopsies, cytological specimens and fine-needle aspiration samples are excluded (Section 7.4.5).

CCI [redacted]

23. AEs should be documented and recorded at each visit using the NCI CTCAE version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.

Table 2. Combination Regimen Escalation and Expansion – Schedule of Activities

Q2W Dosing		Cycle 1 (Days 1-28)				Cycles 2 and 3 (Days 1-28)			Cycle 4 (Days 1 -28)				Cycles 5 and Subsequent Cycles (Days 1-28)			Post Treatment	
	Screen/Baseline (≤28 days)	Day 1	Day 4	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 4	Day 8	Day 15	Day 1	Day 8[25]	Day 15	EOT[26]	Follow-Up[27]
Visit Window (days)*			(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(±2)	(±1)	(±1)	(±2)	(±2)	(±2)	(±2)	(+7)	(+7)
Protocol Activity																	

24. All concomitant medications and non-drug supportive interventions should be recorded on the CRF.
25. Beginning at Cycle 6, Day 8 visits are no longer required.
26. Perform if not completed in the last week (last 6 weeks for tumor assessments).
27. At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, 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.

Table 3. Pharmacokinetic, Immunogenicity, and CCI Pharmacodynamic Assessments – Monotherapy Dosing

Q3W – Monotherapy	Treatment Period																		
	Cycle 1 Only (Days 1 to 21)							Cycle 2 and 3 (Days 1 to 21)		Cycle 4 (Days 1 to 21)							Every Cycle Thereafter		EOT
	Day 1			Day 2 24 hr* Part 1A only)	Day 4 (Part 1A only)	Day 8 (Part 1A only)	Day 15	Day 1		Day 1			Day 2 24 hr* (Part 1A only)	Day 4 (Part 1A only)	Day 8 (Part 1A only)	Day 15	Day 1		
	Pre-dose*	1 hr*	4 hr*					Pre-dose*	1 hr*	Pre-dose*	1 hr*	4 hr*					Pre-dose*	1 hr*	
Visit Window (days)				(±1)	(±1)	(±1)	(±2)						(±1)	(±1)	(±1)	(±2)			(+7)
Protocol Activity																			
PK Samples for PF-06804103 and total antibody[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Samples for PF-06380101[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample for PF-06804103 Immunogenicity[3]	X						X	X		X							X		X
CCI [redacted]																			
[redacted]																			
[redacted]																			
[redacted]																			

* Sampling times are related to the start of infusion; 1 hr samples should be collected immediately at the end of infusion; all samples will be considered protocol compliant if collected ±10 minutes for the 1 hour sample, ±25 minutes for the 4 hour sample, ± 2 hours for the 24 hour sample, and ±2 days for the Day 15 sample. The exact time of the sample collection will be noted on the CRF.

1. Blood samples (4 mL) will be collected for drug concentration measurement of PF-06804103 and total antibody.
2. Blood samples (4 mL) will be collected for measurement of PF-06380101 concentrations.
3. Blood samples (6 mL) will be collected for immunogenicity testing against PF-06804103.

CCI [redacted]

Table 4. Pharmacokinetic, Immunogenicity, and CCI Pharmacodynamic Assessments – Combination Regimen (PF 6804103 in combination with Palbociclib and Letrozole)

Q2W Combination	Treatment Period																						
	Cycle 1 Only (Days 1 to 28)								Cycle 2 and 3 (Days 1 to 28)				Cycle 4 (Days 1 to 28)								Every Cycle Thereafter		EOT
	Day 1			Day 2 24 hr*	Day 4	Day 8	Day 15		Day 1		Day 15		Day 1			Day 2 24 hr*	Day 4	Day 8	Day 15		Day 1		
	Pre-dose*	1 hr*	4 hr*				Pre-dose	1 hr*	Pre-dose*	1 hr*	Pre-dose*	1 hr*	Pre-dose*	1 hr*	4 hr*				Pre-dose	1 hr*	Pre-dose*	1 hr*	
Visit Window (days)				+1	(±1)	(±1)	(±2)				(±2)					(±1)	(±1)	(±1)	(±2)				(+7)
Protocol Activity																							
PK Samples for PF-06804103 and total antibody[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Samples for PF-06380101[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample for PF-06804103 Immunogenicity[3]	X						X		X				X								X		X
CCI																							

* Sampling times are related to the start of infusion; 1 hr samples should be collected at the end of infusion; all samples will be considered protocol compliant if collected ±10 minutes for the 1 hour sample, ±25 minutes for the 4 hour sample, ± 2 hours for the 24 hour sample, ±1 day for the Day 4, Day 8 samples, and ±2 days for the Day 15 sample. The exact time of the sample collection will be noted on the CRF.

Table 4. Pharmacokinetic, Immunogenicity, and Biomarker/Pharmacodynamic Assessments – Combination Regimen (PF 6804103 in combination with Palbociclib and Letrozole)

Q2W Combination	Treatment Period																					
	Cycle 1 Only (Days 1 to 28)								Cycle 2 and 3 (Days 1 to 28)				Cycle 4 (Days 1 to 28)								Every Cycle Thereafter		EOT
	Day 1			Day 2 24 hr*	Day 4	Day 8	Day 15		Day 1		Day 15		Day 1			Day 2 24 hr*	Day 4	Day 8	Day 15		Day 1		
	Pre-dose*	1 hr*	4 hr*				Pre-dose	1 hr*	Pre-dose*	1 hr*	Pre-dose*	1 hr*	Pre-dose*	1 hr*	4 hr*				Pre-dose	1 hr*	Pre-dose*	1 hr*	

1. Blood samples (4 mL) will be collected for drug concentration measurement of PF-06804103 and total antibody.
2. Blood samples (4 mL) will be collected for measurement of PF-06380101 concentrations.
3. Blood samples (6 mL) will be collected for immunogenicity testing against PF-06804103.

[redacted]

1. INTRODUCTION

1.1. Mechanism of Action and Indication

PF-06804103 employs at least 2 different mechanisms of action. The primary mechanism is the targeted delivery of the cytotoxic anti-microtubule auristatin payload to HER2 positive, or HER2 low expressing cells. An additional mechanism of action is inhibition of HER2-mediated signaling in HER2 expressing cancer cells.

PF-06804103 is a HER2 ADC that is currently being investigated in patients with HER2-positive solid tumors or HER2 IHC 1+ or IHC 2+/ISH-BC.

1.2. Background

HER2 is a receptor tyrosine kinase that is involved in the regulation of various cellular functions. Aberrant HER2 receptor activation has been implicated as a driving factor in the tumorigenesis and progression of a number of cancers.[34,27,23]

In BC, overexpression and/or amplification of the HER2 gene, identified by IHC and FISH is observed in 20% to 25% of patients, and these patients are classified as HER2-positive in the clinic. Excessive expression of HER2 often leads to constitutive receptor activation and therefore aggressive tumor growth.[25] Inhibiting HER2 activity with monoclonal antibodies has proven to be an effective therapy for treating HER2 positive metastatic BC.

The frequency of HER2 overexpression in GC ranges from 4.4% to 53.4%, with a mean of 17.9%.[3,25,33,8,11,6,16,4,7,14,20,30,2,13] Similar to breast cancer, HER2-positive status in gastric cancer was associated with decreased survival and clinicopathological features of tumor progression, such as serosal invasion, metastases and higher disease stage.[13] The results clearly set HER2 as a negative prognostic factor, suggesting that HER2 overexpression/amplification is a molecular abnormality that might be associated with the development of gastric cancer.[16,13] To date, one HER2-specific monoclonal antibody has been approved by regulatory agencies for treating HER2-positive GC: trastuzumab. However, that approval was for combination therapy with cisplatin and a fluoropyrimidine (chemotherapy) and there was only an increase in median survival of 2 months over chemotherapy alone.

Although HER2 overexpression has been reported in 13% to 20% of non-small cell lung cancer (NSCLC), 3+ expression is observed only in 2% to 6%.[10,9,36] FISH assessed *HER2* gene amplification is unusual, and it has been reported in 2% to 4% of NSCLCs, mainly of adenocarcinoma-type. Comparably to breast cancer, in spite of the lack of large series, concordance between FISH and IHC 3+ has been confirmed.[9] In our internal IHC analysis of 24 NSCLC specimens, 6 showed 2+/3+ HER2 expression.

To date, 3 HER2-specific monoclonal antibodies have been approved by regulatory agencies for treating HER2-positive metastatic breast cancer: trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1). Although these HER2-targeting therapies have transformed the clinical practice for HER2-positive breast cancer and have resulted in survival benefits, not all patients respond to the therapies. Moreover, the vast majority of

patients who initially respond to the treatment will eventually relapse. This is thought to be due to the high degree of intratumoral heterogeneity of HER2 expression in breast cancer and lack of efficacy of current anti-HER2 therapeutics in tumor cells expressing relatively low levels of HER2. A great deal of effort has been put into developing better anti-HER2 agents that can kill cancer cell populations expressing a broad range of HER2.[15,19] Given the lack of clinical success in developing therapies to treat tumors with relatively low levels of HER2, this remains an area of high unmet medical need.

ADCs are a class of drugs that use antibodies specifically targeting tumor-associated antigens as vehicles to deliver covalently attached small-molecule toxins into cancer cells.[24] T-DM1 is built upon this principle and it consists of trastuzumab coupled with the microtubule poison maytansinoid emtansine (DM1) through a thioether linker.[17,18] Approval of T-DM1 by the FDA in February 2013 is mainly based on the key data derived from a phase III clinical trial investigating the efficacy and safety of T-DM1 in HER2-positive metastatic breast cancer patients.[29] T-DM1 treatment prolonged overall survival by 5 to 6 months with an objective response rate of 44%. While these results are encouraging, they also reveal the limitation of T-DM1 in efficacy. Receptor tyrosine kinases are typically routed to lysosomes for degradation following ligand binding, which is a major, negative feedback mechanism regulating the intensity and duration of receptor activation.[31] Unlike most receptor tyrosine kinases, HER2 has no natural ligand and it appears to be impaired in lysosomal trafficking.[5,26,22] Instead, HER2 is largely recycled back to the plasma membrane following spontaneous endocytosis. Correspondingly, the majority of internalized T-DM1 passively recycles with HER2 back to the cell surface and only a small fraction of T-DM1 is routed to lysosomes for degradation.[5] Since the amount of toxin released into the cytoplasm determines the cell killing potency of an ADC, this may explain the lack of activity with T-DM1 in tumors expressing low levels of HER2. In this regard, it is likely that an improvement in ADC-mediated internalization and lysosomal trafficking would significantly enhance the cytoplasmic delivery of toxins, which may result in the killing of cancer cell populations that express a broader range of HER2.

1.3. Study Rationale

Significant tumor growth control has been observed in preclinical tumor models for various indications, including BC AND GC with HER2 IHC 1+ or IHC 2+/ISH- levels of HER2 expression. This suggests that PF-06804103 may have the potential to provide therapeutic benefit to patients currently ineligible for HER2 targeted therapy. In an effort to identify patients with lower levels of HER2 protein who may respond to PF-06804103, patients with tumors expressing HER2 IHC 1+ or IHC 2+/ISH-will be included and patients with HER2 IHC 0 tumors will continue to be excluded from this study.

1.3.1. Arm C1: PF-06910403 in Combination with Palbociclib Plus Letrozole

ER negatively regulates ERBB2 gene expression and thus HER2 protein production.[37] As an aromatase inhibitor, letrozole negatively regulates ER activation. CDK 4/6 inhibition and HER2 signaling pathways have recently been linked. CDK4/6 inhibition may relieve feedback inhibition on HER2 signaling networks to re-sensitize HER2-expressing tumors to HER2 blockade.[38]

Endocrine treatment is one key component in the treatment of patients with HR-positive, metastatic BC. Combining endocrine therapy with CDKs has proven to enhance the efficacy of endocrine treatment. For example, CDK4/6 in combination with AIs as 1L treatment or fulvestrant as 2L has shown dramatic improvement in PFS.[39] Clinical data has also documented a PFS advantage of adding trastuzumab or lapatinib to AI in postmenopausal women with HR-positive metastatic breast cancer that is HER2-positive. In patients with HER2-positive BC SOC 1L regimen requires the use of HER-directed therapies (herceptin +/- pertuzumab) plus chemotherapy (taxane).[43]

Targeting HER2 IHC 1+ or IHC 2+/ISH- BC with PF-06804103 is expanding the HER2 targeted space to current HER2 IHC 1+ or IHC 2+/ISH- patient population. Furthermore, the recent data suggest combining a CDK 4/6 inhibitor (abemaciclib and HER directed therapy (trastuzumab) and hormonal receptor antagonist (fulvestrant) is superior to either abemaciclib and trastuzumab or trastuzumab and SOC chemotherapy in HR+, HER2+ 3L BC.[43] Taken together, in this patient population, all 4 classes of drugs may be needed for maximum clinical benefit in 1L BC: 1) HER2-directed therapy, 2) chemotherapy (anti-microtubule agent), 3) CDK4/6 inhibitor, 4) endocrine therapy. Another, similar HER2 ADC platform using a cleavable linker along with a cytotoxic (topoisomerase inhibitor) payload has demonstrated substantial clinical antitumor activity and an acceptable safety profile in heavily pretreated HER2 IHC 1+ or IHC 2+/ISH- BC.[41] Therefore, adding a HER2 targeting with a cytotoxic (chemotherapy) component to an antihormonal agent and a CDK4/6 inhibitor in HR-positive HER2 IHC 1+ or IHC 2+/ISH- BC patients is expected to enhance clinical efficacy and decrease the risk of developing resistance.

In this study, patients with HR-positive HER2 IHC 1+ or IHC 2+/ISH- BC will receive PF-06804103 (an anti HER2-ADC consisting of an auristatin anti-microtubulin inhibitor payload site-specifically conjugated onto a Herceptin molecule using a cleavable linker) as combination therapy with an aromatase inhibitor (letrozole) and a CDK4/6 inhibitor (palbociclib) as 1L treatment.

More information about the known and expected benefits and risks and reasonably expected AEs of PF-06804103 may be found in the IB, which is the SRSD for this study.

More information about palbociclib may be found in the IB, which is the SRSD for this study and information about letrozole may be found in the EU Summary of Product Characteristics, which is the SRSD for this study.

1.4. Nonclinical Pharmacology and Safety

The nonclinical safety profile of PF-06804103 has been well characterized. Studies conducted with PF-06804103 were consistent with the ICH S6 (R1) and ICH S9 Guidelines and included a tissue cross-reactivity study in normal tissues of cynomolgus monkeys and human tissues, and exploratory and/or pivotal toxicity studies in rats and/or monkeys. In addition, repeat-dose toxicity studies were conducted in Wistar Han rats with the unconjugated auristatin payload (Aur0101; PF-06380101) as well as a hERG assay and genotoxicity assays.

The pivotal GLP study was conducted in the cynomolgus monkey, the most relevant species, and the proposed route of clinical administration, IV dosing. The major findings in the repeat dose toxicity studies were observed in the bone marrow/hematopoietic system, lung, eye, and reproductive organs. After a 6-week recovery, findings in the lung and ovary did not recover; findings in the eye and at the injection site partially recovered, and recovery of testicular findings could not be assessed as males were not included in the recovery phase due to unscheduled euthanasia. The HNSTD in the pivotal monkey study was defined as 3 mg/kg/dose.

There was no definitive evidence for HER2-dependent effects in the findings from exploratory and pivotal monkey toxicity studies and all effects were considered to be target-independent toxicity arising from payload released in circulation and/or nonspecific uptake of the ADC/payload.

The potential cross-reactivity of PF-06804103 (1 μg/mL and 5 μg/mL) with cryosections of human and cynomolgus monkey tissues was evaluated and showed generally comparable staining across human and monkey tissues. PF-06804103 was also generally consistent with reported sites of HER2 expression,[21] and no unexpected tissue cross reactivity was observed.

For additional information about PF-06904103 refer to the IB.

1.5. Starting Dose Rationale

1.5.1. Part 1A – Monotherapy Dose Escalation

The selection of the monotherapy starting dose for Part 1A is based on the preclinical toxicology results in accordance with the ICH S9 Guidance entitled Nonclinical Evaluation for Anticancer Pharmaceuticals. The cynomolgus monkey was considered the most appropriate species for determining the proposed starting dose in patients. The HNSTD in the pivotal monkey study was 3 mg/kg/dose.

The proposed starting dose of 0.15 mg/kg given as an IV infusion Q3W represents approximately 1/6th of monkey HNSTD (based on human equivalent dose normalized to body surface area).

1.5.2. Part 1B – Combination Regimen Dose Escalation

The starting dose level of PF-06804103 is planned to be at the equivalent to monotherapy Part 2 dose minus 1 and was selected based on potential DDI, any overlapping toxicity considerations, and all available clinical, safety, PK, tolerability, and preliminary efficacy data.

Palbociclib is a weak time-dependent inhibitor of CYP3A and is expected to cause a low to moderate increase in exposure for unconjugated payload PF-06804103. Since the monotherapy Part 2 dose minus 1 is 3 mg/kg Q3W, the starting dose of PF-06804103 in Part 1B will be 2 mg/kg Q2W, to yield the same dosing intensity as 3 mg/kg Q3W in monotherapy dosing. The expected maximum Part 1B dose will be 2.7 mg/kg Q2W, to yield the same dosing intensity as 4 mg/kg Q3W monotherapy dosing. Higher doses of PF-06804103 may be tolerated by patients previously untreated with systemic anticancer therapies. For those patients, the maximum Part 1B dose may exceed 2.7 mg/kg QW.

1.5.3. Part 2A – Monotherapy Dose Expansion

Dose levels of PF-06804103 to be administered will be selected following a review of all available safety, tolerability, preliminary efficacy, and PK data collected in Part 1A. The planned Part 2 monotherapy doses for PF-06804103 are 3.0 mg/kg/ and 4.0 mg/kg Q3W.

1.5.4. Part 2B – Combination Dose Regimen Expansion

The SOC administration of palbociclib is in 28-day cycles, the dose level selection of PF-06804103 Q2W will be based on all available clinical, safety, tolerability, preliminary efficacy, and PK data from Part 1B. The anticipated Part 2 combination dose for PF-06804103 is 2.7 mg/kg Q2W.

2. STUDY OBJECTIVES AND ENDPOINTS

Objective:	Endpoint:
Primary	
To characterize the DLTs of escalating levels of PF-06804103 To assess the safety and tolerability of PF-06804103 To determine the RP2D for PF-06804103 as monotherapy To determine the RP2D for PF-06804103 in combination with palbociclib and letrozole	First cycle (21 days) DLTs – Part 1A First cycle (28 days) DLTs – Part 1B All available safety data including: AEs, SAEs, and clinically meaningful abnormalities in laboratory values and vital signs
Part 2: To investigate preliminary antitumor activity	Part 2 y: OR, as assessed using RECIST version 1.1. Time-to-event endpoints: DR, PFS, TTP
Secondary	
Objective	**Endpoint**
To characterize the single and multiple dose PK of PF-06804103 ADC, total antibody and unconjugated payload (PF-06380101).	SD and MD PK parameters of PF-06804103 ADC, total antibody and unconjugated payload (PF-06380101).
To evaluate the immunogenicity of PF-06804103	Incidence and titers of ADA and NAbs against PF-06804103
To document antitumor activity	OR, as assessed using RECIST version 1.1. Time-to-event endpoints: DR, PFS, TTP – Part 1
To explore preliminary antitumor activity in patients that HER2 positive GC	HER2 expression levels in pre-treatment tumor biopsies via IHC and ISH

CCI	
CCI	
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3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, open-label, multicenter, multiple dose, safety, PK, and PD study of PF-06804103 in adult patients with HER2-positive solid tumors (BC and GC [Part 1A only]) and in postmenopausal patients with HR-positive HER2 IHC 1+ or IHC 2+/ISH- BC. Part 1A and 1B will evaluate escalating doses of PF-06804103 as monotherapy and as part of a combination regimen, respectively. Part 2A and Part 2B will evaluate selected doses of PF-06804103 in expansion cohorts as monotherapy and in a combination regimen, respectively.

In Part 1A, patients with HER2-positive BC or HER-positive GC will receive escalating doses of PF-06804103 starting at 0.15 mg/kg, Q3W in a 21-day cycle to estimate the dose level of PF-06804103 to be administered in Part 2A.

In Part 1B, postmenopausal patients with HR-positive HER2 IHC 1+ or IHC 2+/ISH- BC will receive escalating doses of PF-06804103 starting at the dose equivalent to the recommended monotherapy Q3W Part 2 dose minus 1 dose, Q2W in a 28-day cycle, administered in combination with SOC doses of palbociclib and letrozole (as per local and regional guidelines). Data collected during Part 1B will inform the dose levels selected for dose expansion in Part 2B.

In Part 2A, HER2-positive BC patients in 3L setting will be randomly assigned to receive 3 mg/kg or 4 mg/kg doses of PF-06804103 administered as monotherapy Q3W to further evaluate safety, efficacy, and to evaluate the benefit/risk of 3 mg/kg and 4 mg/kg Q3W in a larger population to support optimal dose selection. Also in Part 2A, HR-positive HER2 IHC 1+ or IHC 2+/ISH- BC patients in 2L setting will receive 4 mg/kg of PF-06804103 administered as monotherapy Q3W. A lower dose (eg., 3 mg/kg) may be tested if the observed toxicity of 4 mg/kg Q3W is determined to be too high.

In Part 2B, patients with HR-positive HER2 IHC 1+ or IHC 2+/ISH- BC in the 1L setting will receive the selected PF-06804103 dose administered Q2W (Part 1B) in a 28-day cycle in combination with SOC doses of palbociclib and letrozole (as per local and regional guidelines).

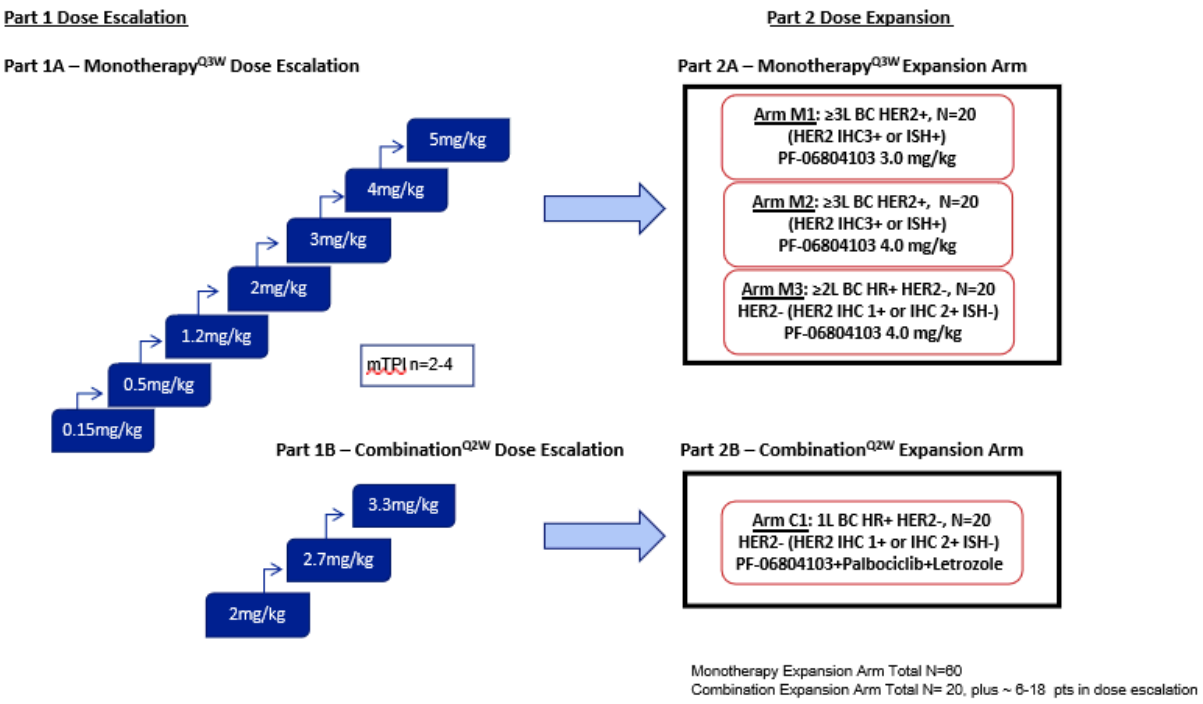
Approximately 148 patients are expected to be enrolled in the study overall. The actual number of patients enrolled will depend on the tolerability of PF-6804103 and the number of dose levels required to identify the MTD and select dose levels for Part 2 of the study.

Treatment with investigational products will continue until either disease progression, patient refusal, or unacceptable toxicity occurs, whichever occurs first, unless the investigator and medical monitor agree to treatment beyond progression based on individual benefit/risk assessments.

In both study parts, the proposed dose levels, schedules, and PK time points may be reconsidered based on emerging safety and PK data. A dose level or treatment arm may be

discontinued at any time depending on the totality of the data including, but not limited to the evaluation of all available clinical, safety, PK, PD, and preliminary efficacy results.

Figure 1. Overall Study Design



3.1.1. Criteria for Dose Escalation

3.1.1.1. Part 1A Monotherapy Dose Escalation

PF-06804103 will be administered as an IV infusion every 21 days at a starting dose of 0.15 mg/kg, dose escalation is planned as described in Table 5. Additional dose levels, or intermediate doses may be explored, if appropriate based on emerging clinical, safety, PK, or PD data.

A mTPI method targeting a DLT rate of approximately 27.5% with an equivalence interval of (22.5%, 32.5%) will be utilized in Part 1 of the study. Patients will be enrolled in cohorts of 2 to 4 patients. Intra-patient dose escalation is not permitted.

Table 5. Part 1A - PF 06804103 Dose Escalation Levels

Dose Level	PF-06804103 Dose (mg/kg)*
1 (Starting Dose)	0.15
2	0.5
3	1.2
4	2.0
5	3.0

Table 5. Part 1A - PF 06804103 Dose Escalation Levels

Dose Level	PF-06804103 Dose (mg/kg)*
6	4.0
7	5.0
8	6.0
9**	n

*Intermediate doses may be evaluated.
**If needed, higher doses may be explored.

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current dose level to determine one of the following dose-finding decisions: the subsequent dose should be escalated, maintained at the current dose, or de-escalated in the next cohort, or the trial should be terminated (Table 6).

Table 6. Decision Rules – Part 1A and Part 1B

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

Actions to be taken:
D=De-escalate the dose; E=Escalate the dose; S=Stay at the dose.
U=Unacceptable toxicity.

In principle, all patients must be evaluated for a minimum period of 21 days. If a patient withdraws from the study before Day 21 for reasons other than drug-related toxicity, another patient may be enrolled to replace that patient in the current cohort. However, if a patient discontinues close to Day 21 for reasons other than toxicity and due to an evident

non-drug-related event, the patient may be deemed evaluable for safety if the investigators and sponsor agree that the patient is evaluable for the DLT safety observation.

The dose escalation in Part 1A of the study will stop if any of the following criteria is met:

- the maximum sample size in Part 1 has been achieved;
- at least 9 patients have been accumulated on a dose that is predicted to be the MTD per the mTPI method;
- all doses explored appear to be overly toxic, and the MTD cannot be determined.

There will be a minimum 48-hour interval between the first dose administered to each of the initial patients (ie, patients contributing to initial DLT evaluation) enrolled at a new dose level. Initially, up to 4 patients will be treated; occasionally, due to logistical/clinical reasons, more than 4, but, no more than 6, patients may be enrolled in each cohort for the initial DLT evaluation. In addition, dose cohorts with an acceptable safety profile may be expanded up to n=15 to further assess safety, pharmacokinetics or pharmacodynamics. Decisions to enroll additional patients at dose levels already cleared for safety will be based on the clinical judgment of the investigators and the sponsor considering all evaluable safety, PK, dose discontinuations, dose reductions, and PD data.

3.1.1.2. Part 1B – Combination Regimen Dose Escalation

Dose escalation in the combination regimen will also follow the mTPI design. PF-06804103 will be administered as an IV infusion every 14 days in combination with SOC oral palbociclib and oral letrozole. Dose escalation up to 3.3 mg/kg Q2W or de-escalation (Table 7) including higher, intermediate, or lower doses may be evaluated based on all available clinical, safety, PK, and/or PD data. If further evaluation is needed, the number of dose levels may be expanded. Intra-patient dose escalation is not permitted

The combination regimen evaluated in Part 1B will be administered to patients with 1L BC HR-positive HER2 IHC 1+ or IHC 2+/ISH-. The actual number of patients enrolled will depend on the tolerability of PF-06804103 at each of dose level when administered in combination with palbociclib and letrozole.

All patients will be evaluated for a minimum period of 28 days. If a patient withdraws from the study before Day 28 for reasons other than drug related toxicity, the patient is not evaluable for the DLT observation period, and the patient will be replaced.

Details on IP administration are provided in Section 5.4.2 (PF-06804103) Section 5.4.3 (palbociclib), and Section 5.4.4 (letrozole).

Table 7. Part 1B - PF 06804103 Dose Escalation Levels

Dose Level	PF-06804103 Dose (mg/kg) Q2W*
-1	1.3
1 (Starting Dose)	2.0
2	2.7
3	3.3

*Intermediate, higher or lower doses may be explored.

Dose escalation in Part 1 B will stop if any of the following criteria is met:

- the maximum sample size has been achieved;
- at least 6 (Part 1B) patients have been administered a dose that is predicted to be the MTD per mTPI;
- all doses explored appear to be overly toxic, and the MTD cannot be determined.

3.1.1.3. Part 2A – Monotherapy Dose Expansion

PF-06804103 will be evaluated as monotherapy when administered as described below:

- Arm M1: ≥3L BC HER2-positive (HER2 IHC 3+ or ISH+) 3 mg/kg Q3W
- Arm M2: ≥3L BC HER2-positive (HER2 IHC 3+ or ISH+) 4 mg/kg Q3W
- Arm M3: ≥2L BC HR-positive, HER2 IHC 1+ or IHC 2+/ISH- 4 mg/kg Q3W

3.1.1.4. Part 2B – Combination Regimen Dose Expansion

The dose level of PF-06804103 to be administered in Part 2B will be selected based on the dose level determined in Part 1B and all available clinical, safety, preliminary efficacy, PK, and PD data and will be administered with palbociclib and letrozole to the patients described below:

- Arm C1: BC 1L, postmenopausal, HR-positive HER2 IHC 1+ or IHC 2+/ISH-, PF-06804103 Q2W with SOC regiment for palbociclib and letrozole

Table 8. Planned Dose Levels for Part 2B

Arm	Regimen		
	PF-06804103	**Palbociclib[1]**	**Letrozole**
C1	Dose TBD mg/kg IV Q2W[2]	125 mg PO QD for 3 weeks[1] repeat every 28 days	2.5 mg PO QD on Days 1 through 28

1. 3 weeks on followed by 1 week off.
2. PF-06804103 dose level to be administered in combination with palbociclib and letrozole to be established from Part 1B.

Detailed sample size information is provided in Section 9.3.

3.2. Dose Limiting Toxicity Definition

Severity of AEs will be graded according to CTCAE version 4.03. For the purpose of dose escalation, any of the following AEs occurring in the first cycle of treatment will be classified as DLTs, unless there is a clear alternative explanation:

Part 1A

Hematologic:

- Grade 4 neutropenia lasting >7 days;
- Febrile neutropenia defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour);
- Grade ≥3 neutropenic infection;
- Grade ≥3 thrombocytopenia with bleeding;
- Thrombocytopenia defined as:
  - any <10,000/mm^3 (or ≥100 x 10^9/L)
  - or 10,000 /mm^3 or (≥100 x 10^9/L) to 25,000 mm^3
  - (or ≥100 x 10^9/L for) >5 days.

Non-hematologic:

- Grade ≥3 toxicities, that are considered clinically significant, except the following:
  - Grade 3 nausea, vomiting or diarrhea lasting <72 hours with adequate antiemetic or other supportive care;
  - Grade ≥3 electrolyte abnormality lasting <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions;
  - Grade ≥3 amylase or lipase that is not associated with symptoms or clinical manifestations or pancreatitis.
- Delay by more than 2 weeks in receiving the next scheduled cycle due to persisting treatment related toxicities. Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade ≤1 or baseline, only after discussion between the investigator and sponsor.
- Concurrent AST or ALT >3x ULN and total bilirubin >2x ULN (potential Hy's law case, (Section 8.4.1).
- Any Grade 5 event not clearly due to underlying disease or extraneous causes.

Part 1B

A DLT is defined as any of the following TEAEs occurring during the first cycle of treatment and considered possibly related to the combination of PF-06804103 plus palbociclib and letrozole:

Hematologic:

- A delay greater than 1 week in administration of the next scheduled dose of study treatment due to persistent treatment-related toxicities (eg, platelet count and ANC of Grade >3 unless the criteria below are met during the DLT observation period):
- Grade 4 neutropenia lasting >7 days;
- Febrile neutropenia (defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour);
- Grade ≥3 neutropenic infection;
- Grade ≥3 thrombocytopenia with bleeding;

- thrombocytopenia (defined as):
  - any <10,000/mm^3;
  - 10,000 to 25,000/mm^3 for >5 days.

Non-hematologic:

- Grade ≥3 toxicities, that are considered clinically significant, except the following:
  - Grade 3 nausea, vomiting or diarrhea lasting <72 hours with adequate antiemetic or other supportive care;
  - Grade ≥3 electrolyte abnormality lasting <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions;
  - Grade ≥3 amylase or lipase that is not associated with symptoms or clinical manifestations or pancreatitis.
- Grade 3 QTc prolongation (QTc >msec) despite correction of reversible causes:
  - In an asymptomatic patient, Grade 3 QTc prolongation (QTc >500 msec) first required repeat testing, re-evaluation by a qualified person, and correction of reversible causes such as electrolyte abnormalities or hypoxia for confirmation.
- Delay by >2 week in receiving the next scheduled dose of any study treatment due to persisting treatment-related toxicities. Patients deriving clinical benefit from study treatment may continue on study at a reduced dose following recovery of the AE to Grade ≤1 or baseline, only after discussion between the investigator and sponsor.
- Inability to administer at least 80% of the planned palbociclib or letrozole doses during Cycle 1 due to toxicity related to the study treatment.
- Inability to administer 100% of the planned dose of PF 06804103 during Cycle 1 due to toxicity related to the study treatment.
- Concurrent AST or ALT >3x ULN and total bilirubin >2x ULN (potential Hy's law case (Section 8.4.1).
- Any Grade 5 event not clearly due to underlying disease or extraneous causes.

In addition, clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by the sponsor and the investigators. All DLTs need to represent a clinically significant shift from baseline.

Grade ≥3 infusion reactions, allergic reactions, or anaphylaxis will not be considered DLTs, as they are unlikely dose related, but may be a reason for study discontinuation and should be reviewed with the sponsor. If Grade ≥3 infusion reactions occur in ≥2 of the first 10 patients at any dose level, or if the occurrence is ≥5% thereafter, a mandatory pre-treatment regimen for all new patients will be implemented. The incidence of Grade 1 and Grade 2 reactions will also be considered. If a total rate of >10% all-grade infusion or allergic reactions is observed, a mandatory pre-treatment regimen for all new patients will be implemented.

All AEs meeting DLT criteria are considered DLTs regardless of baseline .

3.3. Maximum Tolerated Dose Definition

The estimated MTD is the dose level associated with a target DLT rate of approximately 27.5% with an equivalence interval of (22.5%, 32.5%). Due to the discreteness of the dose levels and in the interest of the safety of patients, the estimated MTD is the highest tested dose level with DLT rate ≤ approximately 32.5%. Late onset toxicities which occur outside the DLT observation period may be used in determination of the MTD.

3.4. Recommended Phase 2 Dose Definition

The RP2D is the dose chosen for further investigation based on Phase 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

4. PATIENT ELIGIBILITY CRITERIA

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

4.1. Inclusion Criteria

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

4.1.1. General Study Inclusion Criteria

1. ECOG Performance Status of 0 or 1 (Appendix 2)

2. Adequate bone marrow function including:

   - 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.

3. Adequate renal function, including:

    - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

4. Adequate liver function, including:

    - Total serum bilirubin ≤1.5 x ULN (≤3.0 x ULN if Gilbert's disease);

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

    - ALP ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).

5. Resolution of acute effects of any prior therapy to baseline severity or to Grade ≤1 (NCI CTCAE, version 4.03), excluding AEs not constituting a safety risk as determined by the investigator.

6. Females of childbearing potential who have a negative serum or urine pregnancy test at screening.

7. Females of nonchildbearing potential must meet at least 1 of the following criteria:

    - Postmenopausal, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; have a serum FSH level confirming the postmenopausal state;

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    - Have medically confirmed ovarian failure.

Note: All other female patients (including those with tubal ligations) are considered to be of childbearing potential.

8. Evidence of a signed and dated ICD indicating that the patient has been informed of all pertinent aspects of the study

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

4.1.2. Inclusion Criteria for Part 1A – Monotherapy Dose Escalation

1. Male or female patients age ≥18 years (or age ≥19 years where required by local regulations).

2. Advanced/unresectable or metastatic HER2-positive BC or metastatic HER2-positive adenocarcinoma of the stomach or esophagogastric junction that is refractory to or intolerable with standard therapy or for which no standard therapy is available.

3. Documented histologically or cytologically confirmed diagnosis of HER2 positive BC or metastatic HER2-positive adenocarcinoma of the stomach or esophagogastric junction based on local laboratory results, defined according to the ASCO Guidelines.[32]

4. Hemoglobin-adjusted DLco ≥60% predicted.

5. Documentation of HER2 IHC 3+ or ISH+ status as described in Appendix 3:

4.1.2.1. Inclusion Criteria for Part 2A – Monotherapy Dose Expansion Arms M1 and M2

1. Adult female patients age ≥18 years (or age ≥19 years where required by local regulations).

2. Advanced/unresectable or metastatic HER2-positive BC that is refractory to or intolerable with standard therapy or for which no standard therapy is available.

3. Documented HER2-positive BC histologically or cytologically defined as either HER2 IHC 3+ or ISH+ based on local laboratory results. Documentation of HER2 IHC and/or ISH status per Appendix 3 is required.

4. At least 1 measurable lesion, not previously irradiated, as defined by RECIST version 1.1.

5. Available archival tumor biopsy sample, either FFPE tumor tissue block or unstained slides, for retrospective assessment for HER2 expression. A fresh biopsy sample must be provided (if clinically feasible) if archival material is not available. (See Table 2, Footnote 20, and Section 7.4.5.

4.1.2.2. Inclusion Criteria for Part 2A – Monotherapy Dose Expansion Arm M3

1. Adult female patients age ≥18 years (or ≥19 years where required by local regulations).

2. Advanced/unresectable or metastatic HER2 IHC 1+ or IHC 2+/ISH- BC that has progressed on at least 1 prior line of systemic therapy including a hormonal based regimen.

3. Documented HER2 IHC 1+ or IHC 2+/ISH- BC histologically or cytologically defined as either HER2 IHC 1+ or IHC 2+/ISH- based on local laboratory results. Documentation of HER2 IHC and/or ISH status per Appendix 3 is required.

4. At least 1 measurable lesion, not previously irradiated, as defined by RECIST v1.1.

5. Documentation of histologically or cytologically confirmed diagnosis of estrogen-receptor positive or progesterone-receptor positive BC based on local laboratory results.

6. Available archival tumor biopsy sample, either FFPE tumor tissue block or unstained slides, for retrospective assessment for HER2 expression. A fresh biopsy sample must be provided (if clinically feasible) if archival material is not available. (Section 7.4.5).

4.1.3. Inclusion Criteria for Part 1B and Part 2B - Combination Regimen Dose Escalation and Expansion:

1. Adult female patients age ≥18 years (or age ≥19 years where required by local regulations).

2. Postmenopausal women, defined as:

    - prior bilateral surgical oophorectomy, **or**
    - medically confirmed postmenopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months or FSH and estradiol blood levels in their respective postmenopausal ranges with no alternative pathological or physiological cause.

3. Advanced/unresectable or metastatic HER2 IHC 1+ or IHC 2+/ISH- BC previously untreated with any systemic anti-cancer therapy.

4. Documentation of histologically or cytologically confirmed diagnosis of HER2 IHC 1+ or IHC 2+/ISH- BC based on local laboratory results. Documentation of HER2 IHC and/or ISH status as described in Appendix 3.

5. Documentation of histologically or cytologically confirmed diagnosis of estrogen-receptor positive or progesterone-receptor positive BC based on local laboratory results.

6. A fresh biopsy sample must be provided (Section 7.4.5.2).

4.2. Exclusion Criteria

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

4.2.1. General Study Exclusion Criteria

1. Patients with HER2 IHC 0 as defined in Appendix 3.

2. Symptomatic brain metastases requiring steroid treatment.

    Note: Patients with previously diagnosed brain metastases are eligible if they have completed treatment and recovered from the acute effects of radiation therapy or surgery prior to study entry, have not taken corticosteroids for at least 4 weeks and are neurologically stable.

3. History of prior malignancy other than the diseases under study within the past 5 years (excluding successfully resected treated basal or squamous cell carcinoma of the skin, or any carcinoma in situ which has been adequately treated.)

4. Major surgery within 4 weeks prior to registration.

5. Radiation therapy within 4 weeks prior to registration.

Note: Palliative radiotherapy to a limited field is allowed after consultation with Pfizer's medical monitor.

6. Exposure to anthracyclines at the cumulative doses listed below:

    - Doxorubicin >500 mg/m^2;
    - Liposomal doxorubicin >500 mg/m^2;
    - Epirubicin >720 mg/m^2;
    - Mitoxantrone >120 mg/m^2;
    - Idarubicin >90 mg/m^2.

    If another anthracycline or more than 1 anthracycline has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.

7. Systemic anticancer therapy within 4 weeks prior to study entry; hormonal therapy <7 days prior to registration; trastuzumab, trastuzumab emtansine, or pertuzumab therapy and/or lapatinib <21 days prior to registration.

    If systemic anticancer therapy was given within 4 weeks, patient may be included if 5 times elimination half-life of drug has passed.

8. Patients with serious pulmonary illness including complications of advanced malignancy which may cause dyspnea at rest or requires supplementary oxygen therapy.

9. Grade 3 hypersensitivity reaction to prior receipt of any antibody therapy.

10. Previous high dose chemotherapy requiring stem cell rescue.

11. Prior irradiation to >25% of the bone marrow.

12. History or active interstitial lung disease, pulmonary fibrosis, or a history of other clinically significant lung diseases.

13. History of, or ongoing, corneal disorders.

14. Active and clinically significant bacterial, fungal, or viral infection, including HBV, HCV, known HIV or AIDS related illnesses.

15. Had had in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure,

cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.

16. Has hypertension (>150/100 mmHg) that cannot be controlled by medications.

17. Has inadequate cardiopulmonary function defined as any of the following: LVEF <50% (by ECHO or MUGA), uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures, clinical history of active hemoptysis; evidence of active pneumonitis during screening; or current unstable ventricular arrhythmia.

18. Has symptomatic hypercalcemia requiring use of bisphosphonate therapy within 21 days prior to registration.

    - Patients who receive bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.

19. Has Grade >1 peripheral neuropathy per NCI CTCAE version 4.03 at the time of registration.

20. Is receiving chronic systemic corticosteroid treatment (topical applications, inhaled sprays, eye drops, local injections of corticosteroids and systemic steroids required for acute medical interventions are allowed).

21. History of intolerance, including Grade 3 infusion reaction or hypersensitivity to trastuzumab, murine proteins, or docetaxel/paclitaxel or known or suspected hypersensitivity to recombinant human or murine proteins.

22. Patients treated within the 7 days prior to randomization with any of the following:

    - Food or drugs that are known to be CYP3A4 inhibitors (ie, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice); The topical use of these mediations (if applicable), such as 2% ketoconazole cream, is allowed.

    - Drugs that are known to be CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort).

23. Participation in other studies involving investigational drugs within 30 days, 5 half-lives or twice the duration of the biological effect of the investigational drug (whichever is longer) prior to study entry.

24. Within the past year, any acute or chronic medical or psychiatric condition, including suicidal ideation, behavior, or a laboratory abnormality, that the investigator determines may make the patient inappropriate for this study, increase the risks associated with participation, investigational product administration, or that could interfere with the interpretation of study results

25. Is a site staff member or family member of site staff directly involved in the conduct of the study, a site staff member otherwise supervised by the investigator, Pfizer employees or family members of a Pfizer employee directly involved in the conduct of the study.

26. Is pregnant or breastfeeding. Fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 90 days (or 180 days for patients enrolled in Korea) after the last dose of investigational product.

4.2.2. Exclusion Criteria Specific to Part 1B and 2B Combination Regimen Dose Escalation and Expansion – Arm C1

1. Prior treatment with any CDK4/6 inhibitor

2. Prior neoadjuvant or adjuvant treatment with a nonsteroidal aromatase inhibitor (ie, anastrozole or letrozole) with disease recurrence while on or within 12 months of completing treatment.

3. Patients treated within the 7 days prior to randomization with drugs that are known to prolong the QT interval (refer to Appendix 6).

4. QTc >480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome, known history of QTc prolongation, or Torsade de Pointes (Appendix 8).

5. Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug (eg, hypocalcemia, hypokalemia, hypomagnesemia).

6. Active inflammatory bowel disease, chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.

7. Known hypersensitivity to letrozole, or any of its excipients.

8. Known hypersensitivity to palbociclib, or any of its excipients.

4.3. Lifestyle Requirements

In this study, fertile male patients and female patients who are of childbearing potential will receive PF-06804103, a compound for which the teratogenic risk is currently unknown. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy

with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 90 days (or 180 days for patients enrolled in Korea) after the last dose of investigational product. The investigator or designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient and his or her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or partner.

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

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing IUD.

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

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

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

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

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 product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff

if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

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

In this study, the investigational products are all study treatments to be administered.

Study treatments in Part 1A included the following:

- PF-06804103 administered IV at a starting dose of 0.15 mg/kg Q3W

Study treatments in Part 1B included the following:

- PF-06804103 will be administered IV at a starting dose of 2 mg/kg Q2W + palbociclib (125 mg) + letrozole (2.5 mg) Q4W

Study treatments in Part 2A included the following:

- Arm M1: PF-06804103 will be administered IV at 3 mg/kg Q3W
- Arm M2: PF-06804103 will be administered IV at 4 mg/kg Q3W
- Arm M3: PF-06804103 will be administered IV at 4 mg/kg Q3W

Study treatments in Part 2B included the following:

- Arm C1: PF-06804103 (TBD) Q2W will be administered IV + palbociclib (125 mg) + letrozole (2.5 mg) Q4W

Details on dose administration and escalation can be found in Section 3.1.

5.1. Allocation to Treatment

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will email a completed Registration Form to the designated sponsor study team member or

designee. The sponsor will assign a patient identification number documenting patient enrollment and will supply this number to the site.

In Parts 1B, 2A, and 2B allocation of patients to treatment groups may be performed through an IRT/IWR system.

No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

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

5.2. Patient Compliance

During dose escalation, all doses of investigational products will be administered by the appropriately designated study staff at the investigational site. During dose expansion, palbociclib and letrozole doses will be self-administered and each dose will be recorded in a patient diary.

The site will complete required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

PF-06804103

PF-06804103 is supplied as a powder for reconstitution and IV administration. Each vial contains 40 mg of PF-06804103, is sealed with a coated stopper and an overseal, and is labeled according to local regulatory requirements.

Palbociclib

Palbociclib is commercially available as 125 mg capsules in High Density Polyethylene (HDPE) bottles, labeled according to local regulatory requirements. The 100 mg, and 75 mg capsules will be available for dose reduction.

Letrozole

Letrozole is commercially available as a bottle of 2.5 mg tablets and is labeled according to local regulatory requirements.

5.3.2. Preparation and Dispensing

See the IP manual, for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Vials are for single-use, single-patient only.

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

5.4. Administration of Investigational Products

Every effort will be made to administer all study drugs on the planned dose schedule. All PF-6804103 will be administered at the investigational site on an outpatient basis. Patients will self-administer oral doses of palbociclib and letrozole at home.

5.4.1. Premedication for PF-06804103

The decision to incorporate pre-medication in all patients will be made following discussions between the sponsor and the investigators. Patients should be pre-treated with acetaminophen and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each PF-06804103 administration.

Suggested starting doses are 650 mg to 1000 mg acetaminophen and 50 mg diphenhydramine (or equivalent of other antihistamine) IV or oral. Two additional doses of acetaminophen may be administered approximately every 4-6 hours after the initial pre-treatment or as needed.

5.4.2. Administration of PF-06804103

In all study parts, PF-06804103 will be administered on Day 1 of each cycle, intravenously over approximately 60 minutes (±15 minutes), on an outpatient basis. A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 21 days for monotherapy dosing and 28 days for combination regimen dosing.

Dose levels for dose escalation are described in Section 3.1.1.1 and Section 3.1.1.2 (monotherapy and combination, respectively). Dose levels for dose expansion are described in Section 3.1.1.3 and Section 3.1.1.4 (monotherapy and combination, respectively). At the discretion of the sponsor, alternative dosing schedules may be explored.

Details for PF-06804103 infusion are provided in the IP manual. The decision to recalculate PF-06804103 dose based on the weight obtained at each cycle can be in accordance with institutional practice; however, if the patient experienced either a weight loss or gain >10% compared to the weight used to calculate the initial dose, the amount of PF-06804103

required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

Each patient may receive PF-06804103 until disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

Recommended dose reductions and dose modification guidelines are provided in Table 14.

5.4.2.1. Infusion-Related Reactions – PF-06804103

In the event of infusion related reactions, investigators should institute treatment measures according to best medical and nursing practice. Monitoring and treatment guidelines are provided in Appendix 5.

In the case of infusion related reactions characterized by fever and chills, and less commonly hypotension, the sponsor should be notified and pre-treatment medication should be administered prior to subsequent infusions (in the case that the patient is able to continue on treatment as per Appendix 5.

5.4.3. Palbociclib Administration

Palbociclib will be administered orally at 125 mg PO QD for 3 weeks followed by a 1-week rest period.

Patients should swallow capsules whole and not manipulate or chew them. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should take their dose at approximately the same time each day and record ingestion in the patient diary.

If a dose is missed, patients should skip that dose, record it as missed, and resume dosing the next day. If vomiting occurs following dosing, the dose should be recorded as missed. If an extra dose is taken in the same day, the next daily dose should be skipped.

Recommended dose reductions and dose modification guidelines are provided in Table 15 and Table 16.

5.4.4. Letrozole Administration

Letrozole will be administered orally at 2.5 mg PO QD on Days 1 through 28.

If a dose is missed, patients should skip that dose, record it as missed, and resume dosing the next day. If vomiting occurs following dosing, the dose should be recorded as missed. If an extra dose is taken in the same day, the next daily dose should be skipped.

Recommended dose reductions and dose modification guidelines are provided in Table 17.

5.4.5. Dosing Delays

Patients experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment interrupted/delayed. In addition, any occurrence of ≥ Grade 2 ejection fraction will require a treatment

interruption/delay. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

Specific guidelines for dose reduction for each IP are provided in Appendix 7.

5.4.5.1. Re-Treatment Criteria

If a treatment interruption continues beyond Day 21 (for monotherapy dosing) or beyond Day 28 (for combination regimen dosing) of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle. Re-treatment following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC ≥1,000/mm^3;
- Platelets count ≥75,000/mm^3;
- Non hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator discretion, Grade ≤2 if not considered a safety risk for the patient).

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

If these conditions are not met, treatment must be delayed by 1 treatment cycle (3 or 4 weeks for monotherapy or combination treatment, respectively) unless otherwise specified in Appendix 7. If, after a treatment cycle delay all toxicities have recovered within the limits described above treatment with PF-06804103 can be resumed.

Initiation of the next cycle can only be delayed by a maximum of 1 treatment cycle (3 or 4 weeks for monotherapy or combination therapy, respectively) . If a persisting toxicity does not allow resumption of PF-06804103 monotherapy within 42 days or resumption of combination therapy within 56 days of Day 1 of the previous cycle, the patient will be discontinued from treatment unless discussed and agreed with the sponsor.

5.4.6. Monotherapy PF-06804103 Dose Modifications

In the event of significant toxicity during PF-06804103 monotherapy or combination therapy dosing may be delayed and/or reduced as described in Appendix 7.

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 reduction, not dose delay, is the preferred management of Grade 2 or 3 peripheral neuropathy, myalgia, arthralgia, or skin toxicity PF-06804103-related AEs. To maintain sufficient drug exposure, dose reductions to dose levels lower than 2 mg/kg Q3W are not recommended. Dose delays during the first 6 cycles are also not recommended. Dose modifications may occur in 1 of 3 ways:

- within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- in the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Recommended PF-06904103 dose level reductions are provided in Table 13, and are intended to be permanent (ie, if the patient's dose is reduced to dose minus 1, it remains at the reduced dose level for the remainder of the study). Dose reductions below 2 mg/kg are not allowed. Dose delays during the first 5 cycles as monotherapy are also not recommended.

Patients requiring more than 2 dose reductions will be discontinued from the treatment and enter the follow-up period, unless otherwise agreed between the investigator and the sponsor. Intrapatient dose re-escalation is not allowed.

5.4.7. Combination Therapy Dose Modifications

To maintain sufficient drug exposure, dose reductions below 1.3 mg/kg Q2W are not recommended. Dose delays during the first 5 cycles as combination therapy are also not recommended.

When combining with palbociclib and letrozole, the treatment schedule (cycle and day for treatment) for PF-06804103 should follow that of palbociclib. If palbociclib treatment is delayed and a new cycle is started for palbociclib, PF-06804103 treatment should also be delayed as well and restart on Day 1 of the new cycle. If PF-06804103 treatment needs to be delayed, the biweekly dose for PF-06804103 should be skipped, as needed, while maintaining the original treatment schedule for palbociclib and letrozole.

5.4.8. Palbociclib Dose Modifications

For AEs related to hematologic toxicities (neutropenia), palbociclib should be reduced to the lowest allowed dose per guidelines before initiating PF-06804103 dose modification.

Dose modifications for palbociclib, including dose interruption and dose reduction should be based on the information provided in Table 15.

In the event of a treatment interruption lasting >4 weeks for reasons other than treatment-related toxicity (eg, non-cancer related surgery), treatment may resume if the investigator and sponsor agree the patient is continuing to benefit from treatment.

Recommended dose reductions and dose modification guidelines are provided in Table 15 and Table 16.

5.4.9. Letrozole Dose Modifications

Recommended dose reductions and dose modification guidelines are provided in Table 17.

5.5. Investigational Product Storage

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

Investigational products should be stored in their original containers and in accordance with the labels.

See the IP manual for storage conditions of the product once reconstituted and/or diluted.

Storage conditions for each IP stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

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

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

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatment(s)

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician. All concomitant treatments, blood products, as well as nondrug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

Since the payload Aur0101/ PF-06380101 is primarily metabolized by CYP3A4, there is a potential that its metabolism may be altered in the presence of potent inhibitors or inducers of CYP3A4. Since Aur0101/ PF-06380101 is a substrate for the P-gp efflux transporter, there is a potential that its metabolism may be altered in the presence of potent inhibitors or inducers of P-gp. As a result, co-administration of PF-06804103 and potent CYP3A/P-gp inhibitors and/or inducers, as listed in Appendix 6, is not recommended. Selection of an alternate concomitant medication with no or minimal enzyme/transporter inhibition and/or induction potential is recommended.

Palbociclib is primarily metabolized by CYP3A and sulfotransferase enzyme SULT2A1 (Section 4.2.1). Co-administration of palbociclib and potent CYP3A inhibitors and /or inducers as listed in Appendix 6 is not recommended. See palbociclib prescribing information (http://labeling.pfizer.com/ShowLabeling.aspx?id=2191#section-7) or refer to palbociclib IB.

Any questions regarding administration of concomitant medications, including alternate concomitant medications, should be directed to the sponsor.

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

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

Palliative radiotherapy on study is permitted for the treatment of painful bone lesions provided the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PF-06804103 with radiotherapy, PF-06804103 treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment after recovery to baseline.

5.7.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available ASCO Guidelines.

5.7.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during Cycle 1, but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO Guidelines.[1]

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

5.7.4. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is not permitted in the first cycle. Primary prophylaxis in subsequent cycles is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not contraindicated (Section 5.7).

5.7.5. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not contraindicated (Section 5.7).

5.7.6. Corticosteroids

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

5.7.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06804103 as monotherapy or combination therapy required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06804103 as monotherapy or combination therapy is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate PF-06804103 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures refer to Table 1 and Table 2 (monotherapy and combination therapy, respectively) and Section 7.

6.2. Study Period

For treatment period procedures, refer to Table 1 and Table 2 (monotherapy and combination therapy, respectively) and Section 7.

6.3. Follow-up Period

Refer to Table 1 and Table 2 (monotherapy and combination therapy, respectively) 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 (Section 8.1.3) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Reasons for withdrawal of study treatment may include:

- objective disease progression;
- global deterioration of health status requiring discontinuation;
- unacceptable toxicity;
- pregnancy;
- significant protocol violation;
- lost to follow-up;
- patient refused further treatment;
- 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;
- refused 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 and document the reason provided in the patient's medical record, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs (if applicable).

If the patient refuses further visits, no further study-specific evaluations should be performed and no additional data should be collected. The investigator should inquire about the reason and document the date and method in which the site was notified in the patient's medical record and in the clinical database. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Withdrawal of consent:

Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

6.4.1. Request to Continue Treatment

If the investigator feels the patient is still deriving benefit from treatment, then in discussion with the sponsor may elect treatment for the patient at the same dose or one dose lower until such benefit no longer exists.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that

he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessments

Safety assessments will include collection of, AEs, SAEs, vital signs and PE, 12-lead ECG, ophthalmic examinations, ECHO/MUGA, DLco evaluation, and laboratory assessments (including pregnancy tests and verification of concomitant treatments).

7.1.1. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female patients of childbearing potential, 2 negative pregnancy tests are required before receiving PF-06804103 (1 negative pregnancy test at screening and 1 at the baseline visit immediately before PF-06804103 administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will then be required at the baseline visit before the patient may receive the study treatment. Pregnancy tests will also be repeated at every treatment cycle during the active treatment period, at the end of study treatment period and follow-up visit to confirm that the patient has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by IRBs) or EC or if required by local regulations. In the case of a positive confirmed pregnancy, the administration of IP will be discontinued.

7.1.2. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness.

7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry samples will be drawn at the time points described in Table 1 (Monotherapy Dose Escalation and Expansion) and Table 2 (Combination Regimen Dose Escalation and Expansion) and analyzed at local laboratories.

Table 9. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis	Pregnancy Test	Unique Screening Labs
Hemoglobin	ALT	PT or INR	Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine	Hepatitis B surface antigen
Platelets	AST				
WBC	Alk Phos				
Absolute Neutrophils	Sodium				Hepatitis B core antibody
Absolute Lymphocytes	Potassium				Hepatitis C antibody
Absolute Monocytes	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)		HIV
Absolute Eosinophils	Chloride				FSH – for post-menopausal women
Absolute Basophils	Total calcium				
	Total bilirubin***				
	BUN or Urea				Estradiol – for postmenopausal women
	Creatinine				
	Uric Acid				
	Glucose (nonfasted)				
	Bicarbonate or CO_2				
	Albumin				
	Phosphorus or Phosphate				
	Amylase				
	Lipase				

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

7.1.4. Vital Signs and Physical Examination

Patients will have a PE to include weight, vital signs, assessment of ECOG performance status and height; height will be measured at screening only.

A complete PE will be performed at Screening and at the EOT visit for each patient and will include an assessment of all body systems (including neurological examination, genitourinary examination is optional). Findings of all PEs should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an AE in the CRF.

Abbreviated PEs should be performed as described in Table 1 (Monotherapy Dose Escalation and Expansion) and Table 2 (Combination Regimen Dose Escalation and Expansion), and on an as needed basis for assessment of AEs. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care.

Vital signs will include measurements of temperature, blood pressure (BP) and pulse rate to be recorded in the supine or seated position and pulse oximetry. On dosing days, BP and PR should be measured prior to administration of the investigational product (pre-dose) and

approximately 1 hour after the start of the infusion (ie, just prior to the end of the infusion). For BP assessment, the same arm (preferably the dominant arm) should preferably be used throughout the trial. A blood pressure cuff, which has been properly sized and calibrated, should be used to measure BP. The use of automated devices for measuring BP is acceptable.

Pulse oximetry should preferably be collected prior to the collection of BP and PR. Oxygen levels should be evaluated on the finger in accordance with the sites standard procedures. A single reading should be collected.

7.1.5. Twelve-Lead Electrocardiogram

Triplicate 12-lead ECGs (with a 10-second rhythm strip) tracing will be recorded for all patients at each time point described in Table 1 (Monotherapy Dose Escalation and Expansion) and Table 2 (Combination Regimen Dose Escalation and Expansion). It is preferable that the machine used has a capacity to calculate the standard intervals automatically. Three consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval (all 3 consecutive ECGs should be performed within a 10-minute timeframe). If the mean QTcF is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the institution for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to 500 msec. Patients will then restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to 500 msec after 3 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

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

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

When ECGs coincide with PK sampling, the ECG should be recorded before PK samples are obtained to allow for collection of the PK at the nominal time.

7.1.6. Echocardiogram or Multigated Acquisition Scan

ECHO or MUGA scans to measure cardiac function will be completed at the times specified in Table 1 (Monotherapy Dose Escalation and Expansion) and Table 2 (Combination Regimen Dose Escalation and Expansion). The same modality used at screening should preferably be used for all subsequent timepoints.

7.1.7. Diffusing Capacity of the Lungs for Carbon Dioxide (DLco)

DLco evaluation will be completed as part of screening procedures using a DLco simulator device and following the site's standard procedures. The DLco percent of predicted value obtained at screening will be assessed for eligibility (patients with a decrease of more than 25% compared to the normal DLco range of 75% to 125% are excluded – Part 1A only). In addition, while the patient is on study, measurement in units of mL/min/mm Hg is required in order to grade toxicity by CTCAE version 4.03 which is necessary for potential dose modifications for toxicity per Appendix 7.

Results should be used in conjunction with the chest CT scans for evaluation of potential pulmonary toxicity.

7.1.8. Ophthalmic Examination

An eye exam, to be performed by an ophthalmologist, will be required at screening. The eye exam is to include Best Corrected Visual Activity (BCVA), Intraocular Pressure (IOP) preferably by Goldmann applanation, Biomicroscopic exam (also called slit lamp exam) to evaluate the Lids/Lashes/Adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, lens, and Dilate fundus exam to evaluate the optic nerve, the vessels, the macula, and the peripheral retina. Further ophthalmic examinations should be guided by specific ocular signs and symptoms should they occur during treatment and follow-up.

7.2. Pharmacokinetics Assessments

Blood samples will be collected from patients for analysis as described in Table 3 (Monotherapy) and Table 4 (Combination Regimen). All efforts should be made to obtain the PK samples at the scheduled nominal time. However, samples obtained within the protocol specified time window will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, 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 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.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample

integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite scouting/identification and/or evaluation of the bioanalytical method, CCI [redacted] These data will not be included in the CSR.

7.2.1. Serum Sample Collection for PK Analysis of PF-06804103 ADC, Total Antibody and Unconjugated Payload (PF-06380101)

Blood samples (approximately 4 mL) for measurement of serum PF-06380101 concentrations and blood samples (approximately 4 mL) for determination of PF-06804103 ADC and total antibody concentrations will be collected from patients in appropriately labeled tubes as described in Table 3 (Monotherapy) and Table 4 (Combination Regimen).

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

7.3. Immunogenicity Assessments

Blood samples (6 mL) to provide approximately 3 mL of serum to detect ADA and neutralizing antibody (Nab) against PF-06804103 will be collected into appropriately labeled tubes as described in Table 3 (Monotherapy) and Table 4 (Combination Regimen). Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Study Manual.

Samples will be assayed using validated analytical methods in compliance with Pfizer standard operating procedures. The ADA sample analysis will follow a tiered approach of screening, confirming and titer determination. Samples tested positive for ADA may also be characterized for Nab.

7.4. Biomarker/Pharmacodynamic Assessments

One of the key elements of this study is the possibility to evaluate potential molecular targets that could be modified in vivo by the drug used in this study. The biomarker studies will be used to confirm the MOA, elucidate the PD effects that could support the RP2D, and provide a rationale for combination therapies. The studies may help in the future development of PF-06804103 as monotherapy, or in combination with other compounds.

Table 10 summarizes representative assays to be used and the source of the samples. Samples will be collected as described in Table 3 (Monotherapy) and Table 4 (Combination Regimen). Refer to the Study Manual for details about sample preparation.

Table 10. Pharmacodynamic Summary

Assay	Source
CCI	
Assessment of HER2 expression CCI by IHC and ISH	tumor tissue
CCI	

CCI

CCI

CCI

CCI

CCI

7.4.5. Tumor Biopsies

7.4.5.1. Collection of Biopsy Samples – Part 1

Patient enrollment will be based on prior testing for HER2 positivity by an FDA approved, or locally validated, diagnostic test. Fresh pre-treatment (screening) and Day 1 Cycle 3 (±5 days) biopsy collections are optional. Archival tissue from a prior biopsy will be collected for central evaluation if available.

If collected, the pre-treatment biopsy should be completed after all eligibility criteria have been verified and should be taken from the same lesion, not previously irradiated, CCI [redacted]

Bone biopsies, cytological specimens and fine-needle aspiration samples are excluded.

CCI [redacted]

7.4.5.2. Collection of Biopsy Samples - Part 2

A mandatory fresh pre-treatment, diagnostic quality biopsy, representative of the diagnosed malignancy, will be collected at screening for all patients CCI [redacted] to retrospectively confirm HER2 expression. CCI [redacted] CCI [redacted] An archival sample collected prior to study start may be substituted for the mandatory pre-treatment biopsy if no prior anti-HER2 treatment between the collection of this tumor sample and study start had been administered. If performed, the pre-treatment biopsy should be obtained after all the eligibility criteria have been verified. The mandatory pre-treatment CCI [redacted] should preferably be taken from the same lesion, which has not been previously irradiated

CCI [redacted]

Bone biopsies, cytological specimens and fine-needle aspiration samples are excluded.

CCI [redacted]

7.5. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone X-rays for patients with known or suspected bone metastases. At a minimum, the chest CT scan must be a high-resolution scan with 1 mm slice thickness.

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 described in Table 3 (Monotherapy) and Table 4 (Combination Regimen), whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 6 weeks).

Assessment of response will be made using RECIST version 1.1 (Appendix 4).

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

CCI

CCI

CCI

CCI

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the Clinical Trial SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (Section 8.2.3). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and 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 Safety. Any pertinent additional information must be reported on the Clinical Trial SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the Clinical Trial SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient/legally acceptable representative. In addition, each study patient/ legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events

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

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with Section 8.1.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days; except as indicated below after the last administration of the investigational product.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. SAE Reporting

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the Clinical Trial SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. 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 on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Clinical Trial SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study 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 signs and symptoms;
- changes in physical examination findings;
- hypersensitivity;
- drug abuse;
- drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- drug overdose;
- drug withdrawal;
- drug misuse;
- drug interactions;
- extravasation;
- exposure during pregnancy;
- exposure via breastfeeding;
- medication error;
- occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded 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.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 any protocol-specified 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 recording as an AE.

8.2.3. 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.

Or that is considered to be:

- an important medical event.

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.

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 active collection 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 active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (Section 8.3).

8.2.4. 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 is assessed for medical importance.

Hospitalization does not include the following:

- rehabilitation facilities;
- hospice facilities;
- respite care (eg, caregiver relief);
- skilled nursing facilities;
- nursing homes;
- same-day surgeries (as outpatient/same-day/ambulatory procedures).

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

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

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

- admission exclusively for the administration of blood products.

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

8.3. Severity Assessment

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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a 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.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed tolerators, while those who show transient liver injury, but adapt are termed adaptors. In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are susceptible to progressive and serious liver injury, commonly referred to as DILI. Patients who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an adaptor or are susceptible.

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin elevations (>2 × ULN) by several days or weeks. The increase in total bilirubin typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and total bilirubin values will be elevated within the same lab sample). In rare instances, by the time total bilirubin elevations are detected, AST/ALT values might have decreased. This occurrence is

still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to total bilirubin that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and total bilirubin baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a total bilirubin value >2 × ULN with no evidence of hemolysis and an ALP value <2 × ULN or not available;

- For patients with baseline AST **OR** ALT **OR** total bilirubin values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of total bilirubin above the normal range: total bilirubin level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and total bilirubin separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The patient should return to the investigator 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.

In addition to repeating measurements of AST and ALT and total bilirubin, laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/ INR, total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected.

Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and total bilirubin elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- 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).

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

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

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

Additional information regarding the EDP may be requested by the sponsor. 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 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.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the Clinical Trial SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

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

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
medication errors	all (regardless of whether associated with an AE)	only if associated with an SAE

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- 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.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Clinical Trial SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be

maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Analysis Sets

- The safety analysis set includes all enrolled patients who receive at least one dose of study treatment.
- The full analysis set includes all enrolled patients.
- The PP Analysis Set (evaluable for MTD) includes all enrolled patients who receive at least 1 dose of study treatment and have no major treatment deviations (Section 3.2)during the DLT observation period (eg, first cycle).
- The mITT is the analysis population that will follow the ITT principle and includes all patients who receive least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population may be used for interim analysis and conference presentations when the study is still ongoing.
- The Response Evaluable Population includes all participants who received at least 1 dose of study treatment and had a baseline disease assessment and at least one post baseline disease assessment.
- The PK Parameter Analysis Population is defined as patients who receive at least 1 dose of study treatment, have at least 1 of the PK parameters of interest and who have no major protocol deviations influencing the PK assessment.
- The Immunogenicity Analysis Set includes all patients who receive at least 1 dose of study treatment and have at least 1 ADA sample collected.

[redacted]

9.2. Statistical Methods and Properties

This study has been designed to establish the MTD defined as the dose that yields approximately 27.5% probability of DLT and considers equivalent doses that yield probability of DLT in the interval (equivalence interval) 22.5% to 32.5%. The 27.5% target was chosen based on safety considerations and is considered appropriate based on simulations and expert input. The prior distribution of DLT is set as a beta (0.5,0.5) and the threshold probability for early termination and dose exclusion is set to 0.95 as suggested in

the original mTPI method (Ji et al., 2010).[12] Similarly, doses with an incidence of DLT>32.5% (eg, 4 out of 10) cannot be selected as MTD.

The mTPI design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of three dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.275). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model. Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different trials with different toxicity parameters. More importantly, all the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table. The decision rules to dose escalate (E), no change in dose (S), dose de-escalate (D) or dose de-escalate, unacceptable toxicity (U).

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

The maximum sample size for Part 1 will depend on the underlying dose toxicity profile and variability in actual data realization as described in Section 9.3.

Due to binomial data variability in small samples, DLTs may be observed in a first cohort(s) by chance even when the true Probability (DLT) is fairly low. This could result in the estimated posterior DLT rate to exceed the targeted 27.5% very early in the trial, triggering an early stop when very few patients (2-4) have been treated.

The following table shows the probability of escalating to the next dose level for a range of underlying true DLT rates. For example, for a cohort size of n=3 and for a DLT that occurs in 10% of patients, there is a greater than 90% probability of escalating. Conversely, for a DLT that 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 with DLTs.

Probability of Escalating Dose

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

9.3. Sample Size Determination

This first in patient study is divided in to 2 parts (Section 3.1). Approximately 148 patients are anticipated to be enrolled overall.

Part 1

Patients in Part 1A will participate in dose escalation to determine the Part 2A monotherapy dose level of PF-06804103.

Patients in Part 1B will participate in escalating doses of PF-06804103 administered Q2W in combination with palbociclib and letrozole to determine the Part 2B combination dose level. The actual number of patients enrolled in Part 1 B will depend upon tolerability and the number of dose levels required to identify the MTD of PF-06804103 administered as part of the combination regimen.

CCI [redacted]

CCI [redacted]

CCI [redacted]

9.4. Efficacy Analysis

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, progression date, death date, date of first response and last tumor assessment date, and date of last contact will be listed.

The definition of each response category is provided in Appendix 4.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics

Drug concentrations of PF-06804103 ADC, total antibody and unconjugated payload (PF-06380101) will be measured using validated methods. PK parameters will be determined from the respective concentration-time data using standard non-compartmental methods. Actual sample collection times will be used for the parameter calculations. For PF-06804103 ADC and total antibody, PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{τ}, and if data permit or if considered appropriate, AUC_{inf}, $t_{½}$, CL, V_{ss}, and R_{ac} will be estimated. For unconjugated payload (PF-06380101), PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{τ}, AUC_{inf}, $t_{½}$, and R_{ac} will be calculated as appropriate.

Drug concentrations of PF-06804103 ADC, total antibody and unconjugated payload (PF-06380101) will be summarized graphically and with descriptive statistics by dose, cycle, and the nominal PK sampling time. Non-compartmental PK parameters will be summarized descriptively by dose and cycle.

9.5.2. Pharmacokinetic[redacted] Modeling

PK, efficacy, biomarker, and safety data from both Part 1 and Part 2 may be pooled for PK/[redacted] analyses using appropriate modeling to explore any association between PF-06804103, total antibody and/or payload exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.5.3. Analysis of Biomarkers

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

[redacted]

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA). The statistical

approach will examine correlations of biomarker results with PK parameters and measures of anti-tumor efficacy.

The percentage change from baseline for biomarkers over the period of the study will be tabulated by individual. The mean change from baseline values over time per cohort will also be tabulated. Data will be presented in tabular and/or graphical format and summarized descriptively.

CCI [redacted]

[redacted]

9.5.4. Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of patients with positive ADA and Nab each will be summarized by dose level or by treatment. For patients with positive ADA or Nab, the magnitude (titer), time of onset, and duration of ADA or Nab response will also be described, if data permit.

Potential impact of immunogenicity on PK, clinical responses, and safety/tolerability may be explored, if data warranted.

9.6. Safety Analysis

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

9.6.1. Analysis of the Primary Endpoint

DLT is the primary endpoint of the dose escalation component of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in Section 3. AEs constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints

Adverse Events

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

Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The

analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

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

9.6.3. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline, defined as the assessment at either Cycle 1 Day 1 or screening, whichever is closer to the first dose, and on-treatment ECG data.

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

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Frederica's). Data will be summarized and listed for QT, heart rate , RR interval, PR interval, QRS, QTcF, and by dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

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

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

9.7. Data Monitoring Committee

Not applicable.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCP are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will

allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

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

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

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

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

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

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

12.4. 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 regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the EU is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, 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

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06804103 at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

PCD 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 PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

Publication of study results is also provided for in the CSA between Pfizer and the institution. The defined terms shall have the meanings given to them in the CSA.

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

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43. MonarcHER PhII (ESMO 2019 Congress), available upon request

Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.	
Abbreviation	**Term**
1L	first-line
2L	second-line
3L	third-line
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
AE	adverse event
AI	aromatase inhibitors
AIDS	Acquired Immune Deficiency Syndrome
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphotase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time 0 extrapolated to infinity time
AUC_{last}	area under the concentration-time curve from time 0 to the last measurable concentration
AUC_{τ}	area under the concentration-time curve during the dosing interval
CCI	[redacted]
BC	Breast cancer
BCVA	Best Corrected Visual Acuity
BP	blood pressure
BUN	blood urea nitrogen
C	Cycle
C1D1	cycle 1 day 1
C_{av}	Steady state
CBC	Complete blood count
CD	Cluster of differentiation
CDK	cyclin-dependent kinase
CEP17	Chromosome enumeration probe 17
CCI	[redacted]
CHF	congestive heart failure
CISH	Chromogenic in situ hybridization
CLIA	Clinical Laboratory Improvement Amendments
CK	creatine kinase

CL	clearance
C_{max}	maximum concentration
CNS	central nervous sytem
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
CSA	Clinical supply agreement
CSR	Clinical study report
CT	computed tomography
CTA	clinical trial application
CCI	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DDI	drug-drug-interaction
DILI	Drug induced liver injury
DISH	Dual in situ hybridization
DLco	diffusing capacity of the lungs for carbon monoxide
DLT	dose-limiting toxicity
DM1	maytansinoid emtansine
CCI	[redacted]
DR	duration of response
DS	Daiichi Sankyo
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
eg	for example
EGFR	Epidermal growth factor receptor
EOT	end of treatment
ER	estrogen receptor
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
FSH	follicle-stimulating hormone
FU	fluorouracil
GC	gastric and gastoeosphageal cancer
GCP	Good Clinical Practice
GCLP	Good Clinical Laboratory Practices
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBV	Hepatitis B virus

HCV	hepatitis C virus
hERG	human ether-a-go-go related gene
HER2	Human Epidermal Growth Factor Receptor 2
HNSTD	highest non-severely toxic dose
HR	hormone receptor
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	Identification code
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IOP	intraocular pressure
IP manual	Investigational Product manual
IRB	Institutional Review Board
ISH	in-situ hybridization
ITT	Intent-To-Ttreat
IUD	intrauterine device
IV	intravenous
CCI	[redacted]
LDH	lactate dehydrogenase
LFT	liver function test
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
mTPI	modified toxicity probability interval
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mITT	Modified Intent-To-Treat
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NA	not applicable
Nab	Neutralizing antibody
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NGS	Next-Generation sequencing
OR	Objective Response
ORR	Overall Response Rate
PCD	primary completion date
CCI	[redacted]
PD-1	programmed cell death-protein 1
PD-L1	programmed death-ligand 1

PE	physical exam
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic
PO	per oral
PR	Partial Response
PR	pulse rate
pT	target probability
PT	prothrombin time
QD	daily
QW	once weekly
Q3W	Once every three weeks
QT	time between the start of the Q wave and the end of the T wave
R_{ac}	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
CCI	[redacted]
RP2D	Recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	single dose
SOA	schedule of activities
SOC	standard of care
SRSD	single reference safety document
$t_{1/2}$	terminal elimination half-life
Tbili	total bilirubin
CCI	[redacted]
T-DMI	Ado-trastuzumab emtansine
TKI	Tyrosine kinase inhibitor
T_{max}	time to maximum concentration
TTP	Time to progression
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady state
WBC	white blood cell

Appendix 2. ECOG Performance Status

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

Appendix 3. HER2/IHC Status Descriptions

HER2 IHC 3+ defined as:	• BC: circumferential membrane staining that is complete, intense and in >10% of tumor cells. • GC (Part 1A only): surgical specimen: strong, complete/basolateral or lateral membranous reactivity in 10% of cells. • GC (Part 1A only): biopsy specimen: tumor cell cluster (>5 tumor cells) with strong, complete basolateral or lateral membranous activity irrespective of percentage of tumor cells stained.
HER2 IHC 2+ defined as:	• BC: weak to moderate complete membrane staining observed in >10% of tumor cells. • GC (Part 1A only): surgical specimen: weak to moderate complete basolateral or lateral membranous reactivity in 10% of cells. • GC (Part 1A only): biopsy specimen: tumor cell cluster with weak to moderate, complete basolateral or lateral membranous activity irrespective of percentage of tumor cells stained.
HER2 IHC 1+ defined as:	• BC: incomplete membrane staining that is faint/barely perceptible and in >10% of tumor cells. • GC (Part 1A only): surgical specimen: faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells reactive only in part of their membrane • GC (Part 1A only): biopsy specimen: tumor cell cluster with faint or barely membranous reactivity irrespective of tumor cells stained
HER2 IHC 0 defined as:	• BC: no staining is observed OR membrane staining that is incomplete and is faint/barely perceptible in ≤10% of tumor cells. • GC (Part 1A only): surgical specimen – no reactivity to membranous reactivity in ≤10% of tumor cells. • GC (Part 1A only): biopsy specimen – no reactivity in any tumor cells.

Gene amplification by ISH defined as:	• single probe: average HER2 copy number 6.0 signals/cell; OR • single probe: average HER2 copy number 4.0 and <6.0 signals/cell and concurrent IHC 3-positive and/or concurrent dual-probe ISH Group 1. • dual probe: HER2/chromosome enumeration probe 17 (CEP17) with a ratio 2.0 with an average HER2 copy number >4.0 signals/cell (Group 1). • <4.0 signals/cell (Group 2) and IHC 3-positive. • dual probe HER2/CEP17 ratio <2.0. • average HER2 copy number >6.0 signals/cell (Group 3) requires additional work-up (IHC 3-positive, or IHC2-positive and recount of ISH with observer blinded to previous results, counting at least 20 cells, shows a HER2/CEP17 Ratio <2.0 and an average HER2 signals/cell >6.0). • average HER2 copy number 4.0 and <6.0 signals/cell (Group 4) and IHC 3-positive.

Appendix 4. RECIST (Response Evaluation Criteria in Solid Tumors) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumors: 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 patientive 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 Progressive Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

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

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

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

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

Non-target Disease

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

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

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

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

New Lesions

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

Supplemental Investigations

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

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

Subjective Progression

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

Table 11. Objective Response Status at Each Evaluation

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

Table 12. 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 5. Management of Infusion Related Reactions Including Allergic Reactions, Cytokine Release Syndrome or Anaphylaxis

In the event of infusion related 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 reaction or cytokine release syndrome

- Monitor for worsening condition. If the reaction worsens, stop the infusion. Institute premedication for subsequent infusions as per Section 5.4.

NCI-CTCAE Grade 2 allergic reaction or cytokine release syndrome

- Stop PF-06804103 infusion.
- Administer bronchodilators, oxygen, acetaminophen, and others as medically indicated.
- Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening including respiratory status. If the reaction recurs, stop infusion. Institute premedication for subsequent infusions as per Section 5.4.

NCI-CTCAE Grade 3 or Grade 4 allergic reaction or cytokine release syndrome or anaphylaxis

- A Grade 3 anaphylaxis (hypersensitivity reaction) consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or hypotension.
- A Grade 4 anaphylaxis (hypersensitivity reaction) is a life-threatening event requiring urgent intervention.

Treatment of Grade 3 or Grade 4 allergic reaction, cytokine release syndrome or anaphylaxis

- Stop the PF-06804103 infusion immediately and disconnect infusion tubing from the patient.
- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, and others as medically indicated.

- Monitor closely respiratory and cardiovascular status, be prepared for potential need for intubation.

- Telephone sponsor or designated representative to report an SAE as per Section 7.1.2.

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

Re-treatment following Grade 1 or Grade 2 allergic reactions or cytokine release syndrome

- Once the PF-06804103 infusion rate has been decreased due to an allergic reaction or cytokine release syndrome, it will remain decreased for all subsequent infusions.

- 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-06804103.

- If the patient experiences a Grade 3 or 4 allergic reaction, cytokine release syndrome, or anaphylaxis at any time, the patient should receive no further PF-06804103.

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

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

Appendix 6. Potent CYP3A Inhibitors and Inducers

Potent CYP3A Inhibitors

P-gp Inhibitor	Non-P-gp Inhibitor
elvitegravir/ritonavir (RIT) indinavir or indinavir/RIT lopinavir/RIT nelfinavir ritonavir saquinavir or saquinavir/RIT tipranavir/RIT danoprevir/RIT telaprevir itraconazole ketoconazole clarithromycin mibefradil conivaptan	voriconazole nefazodone cobicistat boceprevir posaconazole telithromycin troleandomycin
List of medications from fda.gov and University of Washington Drug Interaction Database. Potent CYP3A inhibitors are defined as those drugs that increase the AUC of oral midazolam or other CYP3A substrates ≥5-fold.	

Potent CYP3A Inducers

St. John's Wort avasimibe carbamazepine phenytoin rifampin
List of medications from fda.gov. Potent CYP3A inducers are defined as those drugs that decrease the AUC of CYP3A substrates ≥80%.

As the list of CYP and/or P-gp inducers and inhibitors is a dynamic list continually changing when new information becomes available, use the following FDA website when deciding if a concomitant medication is considered a strong CYP3A/P-gp inhibitor and/or inducer: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

Selection of an alternate concomitant medication with no or minimal enzyme inhibition and/or induction potential is recommended.

Appendix 7. Dose Modification Guidelines

Table 13. PF 06804103 Recommend Dose Reductions

PF-06804103 – Monotherapy mg/kg, Q3W	PF-06804103 – Combination Regimen mg/kg, Q2W
4	2.7
3	2.0
2	1.3

Table 14. Dose Modifications for Toxicities Considered Possibly Related to PF-06804103

Toxicity	Action
Grade 3 non-hematologic (including persistent nausea, vomiting, diarrhea despite optimal medical therapy).	• Hold PF-06804103 infusion until recovery to Grade 0-1 or baseline and reduce by 1 dose level. • Discontinue PF-06804103 if a dose delay of greater than 1 cycle (3 or 4 weeks for monotherapy or combination therapy, respectively)is required. • If toxicity reoccurs despite reduction, patient may be dose reduced again by another dose level upon recovery to Grade 0 to 1 or baseline unless the patient is in the first dose group. • Prompt palliative measures are strongly encouraged (eg, anti-emetics).
Grade 4 non-hematologic toxicity, including ejection fraction decrease or persistent nausea, vomiting, diarrhea despite optimal medical therapy.	• Patients who experience Grade 4 non-hematologic toxicities despite intervention should be discontinued from treatment.
Grade 2/3 peripheral neuropathy, myalgia/arthralgia and skin toxicity	• Begin management with dose reduction (not dose delay) • Reduce by 1 dose level. • If Grade 2/3 toxicities persist or reoccur despite reduction, patient may be sequentially dose reduced to the next lower dose level (see Table 5) unless current dose level is ≤ 2 mg/kg Q3W or ≤1.3 mg/kg Q2W. • Maximal allowed dose reductions should be followed before initiating dose delay. Dose delays during the first 6 (monotherapy) or 5 (combination regimen)

Table 14. Dose Modifications for Toxicities Considered Possibly Related to PF-06804103

	cycles are not recommended. • Discontinue PF-06804103 if a dose delay of greater than 1 cycle (3 or 4 weeks for monotherapy or combination therapy, respectively) is required. Retreatment can be considered after discussion with the Sponsor if potential benefit outweighs risk
Grade 4 peripheral sensory neuropathy	• Discontinue PF-06804103
Grade ≥3 peripheral motor neuropathy	• Discontinue PF-06804103
Decrease in LVEF of ≥10% points from baseline for patients with LVEF from 40% to ≤45%.	• Hold PF-06804103 and repeat ECHO/MUGA in 14 or 21 days (Q2W or Q3W, respectively) if absolute decline from baseline is ≥10% until recovery to Grade ≤2 or baseline. • At the discretion of the investigator, the dose may be resumed at the same dose level or reduced by 1 dose level. • If absolute decline from baseline is <10%, continue PF-06804103 and re-evaluate LVEF at the next cycle. • If toxicity recurs, clinically significant cardiac dysfunction or cardiac failure develops or persists, or if significant medical management is required to maintain ejection fraction, discontinue PF-06804103.
Grade 3 left ventricular systolic dysfunction or drop of LVEF to below 40%.	• Hold PF-06804103 and repeat ECHO/MUGA in 14 or 21 days (Q2W or Q3W, respectively) to confirm. • If confirmed, discontinue PF-06804103. • If not confirmed, resume at the current dose or reduce by 1 dose level (at the discretion of the investigator) once recovered to Grade ≤2 or baseline. • Treat and monitor according to standard medical practice.
Grade 2 carbon monoxide diffusing capacity decreased.	• Hold PF-06804103 until recovery to Grade 0 to 1 or baseline and reduce by 1 dose level. • Discontinue PF-06804103 if a dose delay greater than 1 cycle (3 or 4 weeks for monotherapy or combination therapy, respectively) is required. • If toxicity reoccurs, discontinue PF-06804103.

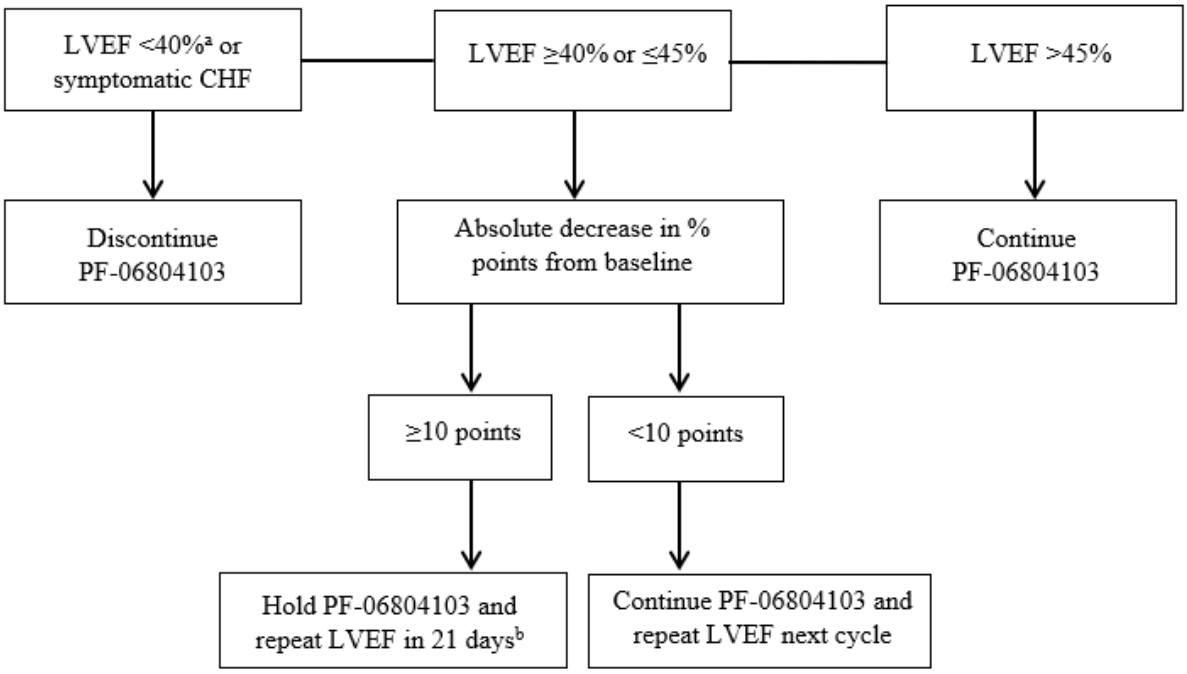
Table 14. Dose Modifications for Toxicities Considered Possibly Related to PF-06804103

Grade 3 carbon monoxide diffusing capacity decreased.	• Discontinue PF-06804103.
Grade ≥3 hepatic toxicity (including serum bilirubin, ALT, AST, alkaline phosphatase).	• Hold PF-06804103 infusion until recovery to Grade 0 to 1 or baseline and reduce by 1 dose level. • Discontinue PF-06804103 if a dose delay greater than 1 cycle (3 or 4 weeks for monotherapy or combination therapy, respectively) is required. If toxicity reoccurs, the dose may be reduced further by another dose level upon recovery to grade 0 to 1 or baseline unless the patient is in the first dose group.
ALT or AST ≥3.0 x ULN concurrent with elevation in bilirubin ≥2.0 x ULN.	• Discontinue PF-06804103.
Hematologic toxicities: Uncomplicated Grade 3 neutropenia (ANC<1000/mm3	• If Grade 3 neutropenia is reported, a CBC should be repeated 1 week later. • Palbociclib should be reduced to the lowest allowed dose (i.e., 75 mg/day) per guidelines (Table 5) before initiating PF 06804103 dose modification. • Dose adjustments to PF-06804103 will only be initiated upon fulfillment of palbociclib dose reduction as described above. • Administration of PF-06804103 should be withheld and initiation of the next cycle delayed until recovery to Grade ≤2 (≥1000/mm^3). • No dose reductions to PF-06804103 are required for first incidence. • Recommended PF-06804103 dose level reductions are provided in Table 12. If toxicity reoccurs despite reduction, the patient may be dose reduced again by another dose level (Table 13) upon recovery to Grade 0 to 1 or baseline unless the current dose is ≤2 mg/kg Q3W or 1.3 mg Q2W).
Hematologic toxicities: • Grade 4 neutropenia, ie, ANC <500/mm^3 (0.5 x 10^9/L) for more than 7 days. • Febrile neutropenia, ie, fever with a single temp >38.3°C or sustained temp ≥38°C for more	• A CBC should be repeated no less than 1 week later. • Palbociclib should be reduced to the lowest allowed dose (i.e., 75 mg/day) per guidelines (Table 5) before initiating PF 06804103 dose modification . • Dose adjustments to PF-06804103 will only be initiated upon fulfillment of palbociclib dose reduction as described above.

Table 14. Dose Modifications for Toxicities Considered Possibly Related to PF-06804103

than 1 hour with ANC <1000/mm^3. • Grade 4 Anemia. • Grade ≥3 Thrombocytopenia with bleeding. Grade 4 Thrombocytopenia, ie, platelets <25,000 mm^3 (25.0 x 10^9/L).	• Hold PF-06804103 until recovery of ANC to ≥1.0 x 10^9/L (1,000 cells/mm^3), platelets ≥75 x 10^9/L (75,000 platelets/mm^3) and hemoglobin to baseline. • Discontinue PF-06804103 if a dose delay of greater than 1 cycle (3 or 4 weeks for monotherapy or combination treatment, respectively) is needed. • If toxicity reoccurs despite dose reduction, dosing may be withheld until recovery and then continued at the same dose, or a further dose reduction by another dose level unless the current dose is <2 mg/kg Q3W or <1.3 mg/kg Q2W.
Other grade 4 hematologic toxicity.	• Hold PF-06804103 until recovery to Grade 0 to 1 or baseline and reduce PF-06804103 dose by 1 dose level. • Discontinue PF-06804103 if a dose delay of greater than 1 cycle (3 or 4 weeks for monotherapy or combination treatment, respectively) is needed. • If toxicity reoccurs despite dose reduction, dosing may be withheld until recovery and then continued at the same dose unless the current dose is <2 mg/kg Q3W or <1.3 mg/kg Q2W.
No recovery of toxicities within 1 cycle (3 or 4 weeks for monotherapy or combination treatment, respectively) of scheduled PF-06804103 infusion.	• Discontinue PF-06804103.

Figure 2. Algorithm for Continuation and Discontinuation of PF-06804103 Based on LVEF Assessments in Patients with LVEF ≥40% or ≤45%



CHF = congestive heart failure; LVEF = left ventricular ejection fraction
Note: LVEF assessment results must be reviewed before the next scheduled PF-06804103 dose
a LVEF <40% can be repeated within 21 days and PF-06804103 should be discontinued if LVEF <40% is confirmed. PF-06804103 should be held while repeat LVEF is obtained.
b After a second consecutive confirmatory result, PF-06804103 should be discontinued if the LVEF is confirmed and if medical management was required in order to correct the LVEF.

Table 15. Dose Modifications for Palbociclib[a] Related Toxicities

Hematologic Toxicity[a]	
Grade 1 or Grade 2	Continue at same dose level.
Grade 3	Day 1 of cycle: Consider repeating complete blood count monitoring 1 week later. Withhold palbociclib and initiate next cycle when recovery to Grade ≤2 (≥1000/mm3). No dose adjustment to palbociclib is required. Day 15 of cycle: If Grade 3, continue palbociclib at current dose to complete cycle and repeat CBC on Day 22. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles. If Grade 4 on **Day 22**, see Grade 4 dose modification guidelines below.
Grade 3 ANC (<1000 to 500/mm3) + Fever ≥38.5ºC and/or infection	Withhold palbociclib and initiate next cycle when recovery to Grade ≤2 (≥1000/mm3). Resume at next lower dose.
Grade 4	Withhold palbociclib and initiate next cycle when recovery to Grade ≤2. Resume at next lower dose.
Non hematologic Toxicity[b]	
Grade 1 or Grade 2	Continue at same dose level.
Grade ≥3 non-hematologic toxicity[c]	• Withhold dose until toxicity is Grade ≤2, then resume treatment at next lower dose. • If the toxicity recurs with Grade 3 severity, withhold dose until toxicity is Grade ≤2 then resume treatment at the next lower dose of the combination or discontinue treatment (at the discretion of the investigator).
Grade 4 non-hematologic toxicity[c]	Discontinue Treatment.
Dose Modifications for Hepatic Impairment • No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). The recommended dose of for patients with severe hepatic impairment (Child-Pugh class C), is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.	

Grading according to NCI CTCAE v. 5.0:

- Grade 1: ANC < LLN - 1500/mm^3;
- Grade 2: ANC 1000 - <1500/mm^3;
- Grade 3: ANC 500 - <1000/mm^3;
- Grade 4: ANC <500/mm^3.

a. Monitor CBC before the start of palbociclib therapy and at the beginning of each cycle, as well as on Day 14 of the first 2 cycles, and as clinically indicated.
b. Table 5 applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, eg, opportunistic infections).

Table 15. Dose Modifications for Palbociclib[a] Related Toxicities

c. Including, nausea, vomiting, diarrhea, and hypertension (only if persisting despite optimal medical treatment).

Table 16. Recommended Dose Level Reductions for Palbociclib

	Available Dose of Palbociclib (mg/day)
Recommended starting dose	125
First dose reduction	100
Second dose reduction	75*

* If further dose reduction below 75 mg/day is required, discontinue the treatment.

Table 17. Dose Levels Reductions for Letrozole

Criteria	**Available Dose of Letrozole (mg)**
	Dose
Recommended starting dose	2.5
First dose reduction	2.5*

* In patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. The recommended dose for such patients is 2.5 mg administered every other day (see prescribing information).

Appendix 8. List of Drugs Known to Predispose Patient to Torsade de Pointes

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S. ®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

*when administered intravenously at high dose (32 mg).

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes

on the University of Arizona CERT website: http://www.crediblemeds.org/. This list is not meant to be considered all inclusive. See website for current list.