Protocol C0541001

PF-06804103

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 SOLID TUMORS

Statistical Analysis Plan (SAP)

Version: Amendment 1

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment 1	Section	Update
	All	Texts taken directly from the protocol are made *italicized* Updated per protocol amendment 4

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol C0541001. This analysis plan is meant to supplement the study protocol. In this document, any text taken directly from the protocol is italicized. Any deviations from this analysis plan will be described in the Clinical Study Report (CSR).

2.1. Study Design

This is a Phase 1, open-label, multicenter, multiple dose, safety, pharmacokinetics (PK), and pharmacodynamics (PD) study of PF-06804103 in adult patients with HER2-positive solid tumors (breast cancer (BC) and gastric cancer (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.

2.1.1. MTD Determination (Part 1)

The estimated MTD is the dose level associated with a target dose limiting toxity (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 will be used in determination of the MTD.

A modified toxicity probability interval (mTPI) method 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.

The planned dose levels in Part 1A monotherapy escalation and Part 1B combination regimen escalation are described in Tables 1A and 1B. *Additional dose levels, or intermediate doses may be explored, if appropriate based on emerging clinical, safety, PK, or PD data.*

Table 1A. 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
6	4.0
7	5.0
8	6.0
9**	n

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

Table 1B. 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.

The modified toxicity probability interval (mTPI) design uses a Bayesian decision-theoretic framework and a beta/binomial hierarchical model to tailor dose-escalation and de-escalation decisions. These rules are conceptually similar to those used by the 3+3 design and all the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table.

The decision rules to "dose escalate" (E), "no change in dose" (S), "dose de-escalate" (D) or "dose de-escalate, unacceptable toxicity" (U) are described below:

Table 2. Decision Rules

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.

For Part 1A*, 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.

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 in Part 1B 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.*

2.1.2. Dose Expansion Phase (Part 2)

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 IHC 1+ or IHC 2+/ISH- 4 mg/kg Q3W*

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*

2.2. 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	

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis or blinding is planned for this study. The final analysis will be conducted after the last subject last visit (LSLV).

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There are no statistical hypotheses. The emphasis of the final analyses will be on estimation of key summary statistics.

4.2. Statistical Decision Rules

4.2.1. Part 1

Decision rules are based on calculating unit probability mass (UPM) of three dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as (0; pT-e1), the over-dosing interval (pT+e2), and the proper-dosing interval (pT-e1, pT+ e2), where e1 and e2 are small fractions. For a target DLT rate of 0.25, the target equivalence interval is (0.225, 0.325). The three dosing intervals are associated with three different dose-escalation decisions (Table 2). The under-dosing interval corresponds to a dose escalation (E), over-dosing corresponds to a dose de-escalation (D), and proper-dosing corresponds to remaining at the current dose (S). Given a dosing interval and a probability distribution, the unit probability mass (UPM) is defined as the ratio of the probability of the interval to the length of the interval. Once the safety assessment is complete for Cycle 1 (ie, 21 days after the first dose), the focus will be on allocation of new subjects to the dose most likely to be an MTD.

The study continues accruing until one of the three stopping conditions below is triggered. The algorithm will stop if any of the following criteria is met:

- The maximum sample size has been achieved.
- MTD has been identified with sufficient accuracy: at least 9 patients have been accumulated on a dose that is currently estimated to be the MTD, or
- All doses explored appear to be overly toxic and the MTD cannot be determined.

Specifically the mTPI approach formalizes stopping rules as follow:

Rule 1 (early termination): if the first dose is too toxic $\rightarrow \quad \Pr(p_1 > p_T / data) > \xi \quad ; \quad \xi = 0.975$

Rule 2 (dose exclusion), if dose= i is too toxic $\rightarrow \quad \Pr(p_i > p_T / data) > \xi \quad ; \quad \xi = 0.975$
then exclude doses $\geq i$

4.2.2. Part 2

Part 2 of this study is intended to confirm the safety and tolerability of the dose selected in Part 1 while assessing the antitumor activity of PF-06804103 in patients with solid tumors.

Analyses may be performed on data from both Part 1 and Part 2 to explore the relationships between PK parameters, safety endpoints, and efficacy endpoints.

5. 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.

Part 2

Patients in Part 2 will participate in monotherapy dose expansion (Part 2A) and in combination regimen expansion (Part 2B]).

Part 2A

Arm M1 and Arm M2 (≥3L BC HER2-positive) and Arm M3 (≥2L BC HR-positive HER2 IHC 1+ or IHC 2+/ISH-: assuming a non informative prior (ie, Jeffrey's prior) if 10 out of 20 participants have tumor response, this would predict a posterior probability (Beta Binomial) equal to 0.82 that the true response is not inferior to the target response rate of 40%.

Part 2B

Arm C1 1L BC HR-positive HER2 IHC 1 + or IHC 2+/ISH-, assuming a noninformative prior (ie, Jeffrey's prior) if 13 out of 20 participants have tumor response, this would predict a posterior probability (Beta Binomial) equal to 0.82 that the true response is not inferior to the target response rate of 55%.

It is anticipated that approximately 60 patients will be enrolled in Part 2A, and 20 patients will be enrolled in Part 2B. The sample size may be modified (up to 40 patients per arm) depending on the totality of the data including but not limited to the evaluation of clinical, safety, PK, PD, and preliminary efficacy.

6. ANALYSIS SETS

Several analysis sets are defined and will be considered for this study.

6.1. Full Analysis Set

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

6.2. 'PER PROTOCOL' Analysis Set (evaluable for MTD)

The per protocol analysis set includes all enrolled patients who receive at least one dose of study treatment and who do not have major treatment deviations during the DLT observation period (e.g., first cycle). Patients with major treatment deviations during the DLT observation period are not evaluable for the MTD assessment and will be replaced as needed to permit MTD estimation. Major treatment deviations include but are not limited to:

- Failure to satisfy major entry criteria (eg, confirmation of the target disease, signed informed consent).
- Administration of less than 80% of the planned dose of PF-06804103, palbociclib or letrozole (provided that the reduction is not due to toxicity attributable to PF-06804103) in Cycle 1.
- Use of other anticancer treatments during the active treatment and disease follow-up phases other than as defined/allowed in this protocol.

6.3. Safety Analysis Set

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

6.4. Modified Intent to Treat (mITT) Population

The modified intent to treat (mITT) is the analysis population that will follow the ITT principle and include patients receiving at least 1 dose of investigational product with adequate baseline assessment and at least 1 determinate post baseline assessment (for SD or Non-CR/Non-PD, at least five weeks after treatment start date), disease progression, or death before the first tumor assessment.

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 31 days prior to and including the date of first dose of study treatment.
- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

The mITT population will be used for analyses and to support conference presentations when the study is still ongoing.

6.5. PK Analysis Set

The PK parameter analysis set is defined as patients who receive at least 1 dose of study treatment and have at least 1 of the PK parameters of interest. If specified clearly, the patients who have major protocol deviations influencing the PK assessment will be excluded.

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for PF-06804103, palbociclib or letrozole.

6.6. Biomarker Analysis Set

The biomarker analysis population is defined as all enrolled patients with at least 1 of the biomarkers evaluated at pre- and/or post-dose.

6.7. Other Analysis Sets

6.7.1. Immunogenicity analysis set

The immunogenicity analysis set includes all patients who receive at least 1 dose of study treatment and have at least 1 ADA sample collected.

6.7.2. Soluble HER2 analysis set

The soluble HER2 concentration analysis set is a subset of the biomarker analysis set including patients who have at least 1 soluble HER2 concentration above the lower limit of quantification.

6.8. Treatment Misallocations

Patients who receive the wrong initial dose for whatever reason will be analyzed according to the initial dose actually received. Patients who receive the wrong dose after the initial dose will be analyzed according to the initial dose received.

6.9. Protocol Deviations

All deviations will be listed in the clinical study report (CSR). Major treatment deviations requiring a patient to be excluded from the MTD evaluaton are listed above in Section 6.2.

7. ENDPOINTS AND COVARIATES

7.1. Efficacy Endpoint(s)

In this first in patient study, anti-tumor activity will include evaluation of objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 by calculating the Overall Response Rate (ORR). Time to event endpoints, including Duration of Response (DR), Progression Free Survival (PFS), and Time to Progression (TPP) will also be evaluated.

The above efficacy endpoints are derived based on the disease response per investigator evaluation on the CRF pages, which is the primary method of documentation of disease.

- **Overall Response (OR) –** or Response Rate (RR) is defined as complete response (CR) or partial response (PR) according to RECIST 1.1 (Appendix 1). Overall response is the best response recorded from first dose until disease progression/recurrence.

- **Progression Free Survival (PFS) -** is defined as the time from Cycle 1 Day 1 (C1D1) to first documentation of disease progression or death due to any cause, whichever occurs first. Patients last known to be 1) alive 2) on treatment or within the post-treatment follow-up period and 3) progression-free, are censored at the date of the last disease assessment that verified lack of disease progression. Patients who start new anti-cancer treatment (drug and non-drug therapy) prior to the end of post-treatment follow-up period and have adequate baseline and on-treatment objective disease assessments without evidence of progressive disease are censored at the date of the last objective disease assessment. Patients with inadequate baseline or no on-study disease assessments are censored at C1D1 unless death occurred prior to the first planned assessment (in which case the death is an event). Patients with documentation of progression or death after an unacceptably long interval (>16 weeks) since the previous disease assessment will be censored at the time of the previous assessment.
- PFS (months) = [progression/death date – C1D1 + 1]/30.3475.

- **Duration of Response:** Time from the date of first documentation of CR or PR to the date of first documentation of objective progression or death due to any cause.

- **Time to progression:** Time from Cycle 1 Day 1 (C1D1) to disease progression

More details of censoring are provided in Appendix 2.

7.2. Safety Endpoints

7.2.1. DLT Definitions

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/mm3 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/mm3 (or ≥100 x 109/L)*
- *or 10,000 /mm3 or (≥100 x 109/L) to 25,000 mm3*
- *(or ≥100 x 109/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/mm3 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/mm3;*

- *10,000 to 25,000/mm3 for >5 days.*

Non hematologic:

- *Grade ≥3 toxicities, that are considered clinically significant, except the following:*

o Grade 3 nausea, vomiting or diarrhea lasting <72 hours with adequate antiemetic or other supportive care;

o Grade ≥3 electrolyte abnormality lasting <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions;

o 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:*

o 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 .

7.2.2. MTD 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.

7.2.3. Recommended Phase 2 Dose (RP2D) Definition

The Recommended Phase 2 Dose (RP2D) is the dose chosen for further study based on Phase 1 results. If the MTD proves to be clinically feasible for long term administration in a reasonable number of patients, such dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

7.2.4. Vital Signs

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. See Schedule of Activities in the protocol for details.

7.2.5. Laboratory Data

The laboratory results will be graded according to the NCI CTCAE v4.03 severity grade. For labs for which an NCI CTCAE v4.03 scale does not exist, the frequency of patients with

values below, within, and above the normal ranges will be summarized by dose. Baseline evaluations for laboratory data are those collected:

- Within 28 days prior to Cycle 1/Day 1.
- Closest but prior to Cycle 1/Day 1 if there is more than one baseline evaluation.

7.2.6. Adverse Events

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 Adverse Events, those with the onset dates occurring during the on-treatment period. The on-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). *The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).* The Safety Analysis Set will be used. Part 1 and Part 2 data will be summarized separately and may also be pooled together for analysis. Pfizer standard on safety data reporting will be followed.

7.2.7. ECG and QTc Interval

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. The analysis will be conducted and summarized as follows:

- The number of patients with maximum change from baseline in QTc (<30, 30-60, and ≥60 ms).

- The number of patients with maximum post-dose (post-baseline) QTc (≤450, 450-≤480, 480-≤500, and >500 ms).

In addition, the number of patients with corrected and uncorrected QT values ≥500 msec will be summarized.

Shift tables will be provided for baseline vs. worst on study QTc (one or more correction method will be used) using absolute value. *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).*

If more than one ECG is collected at a nominal time post dose (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from those triplicate measurements is also ≥500 msec. Changes from baseline will be defined as the change between QTc post dose from Day 0, or the pre-dose values on Day 1.

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

7.2.8. Immunogenicity Endpoints

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.

7.3. PK Endpoints

Blood samples for PK analysis of PF-06804103 (ADC), total antibody, and unconjugated payload will be taken according to the Schedule of Activities given in the protocol. *Drug concentrations of ADC (PF-06804103), total antibody, and unconjugated payload will be measured using validated methods. PK parameters will be determined from the respective concentration time data using standard noncompartmental methods. Actual sample collection times will be used for the parameter calculations. For ADC and total antibody, PK parameters including maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration time curve over 1 dosing interval (AUC_{τ}), area under the concentration time curve from time 0 to the last measurable concentration (AUC_{last}), and if data permit or if considered appropriate, area under the concentration-time curve from*

time 0 extrapolated to infinity time (AUC_{inf}), terminal elimination half-life ($t_{½}$), clearance (CL), volume of distribution at steady state (V_{ss}), and accumulation ratio (R_{ac}) will be calculated. For unconjugated payload, PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{inf}, AUC_{τ}, $t_{½}$, , and R_{ac} will be calculated as appropriate.

PK parameters will be derived from the concentration-time data as follows:

Parameter	Definition	Method of Determination
AUC_{last}	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration	Linear/Log trapezoidal method
AUC_{τ}	Area under the concentration-time profile from time zero to the time τ, the dosing interval	Linear/Log trapezoidal method
AUC_{inf}	Area under the concentration-time profile from time zero extrapolated to infinite time	$AUC_{(0\text{-}t[last])}$ + (Clast*/kel), where Clast* is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis.
AUC_{τ} (dn)	Dose-normalized AUC_{τ}	AUC_{τ} /Dose
AUC_{inf} (dn)	Dose-normalized AUC_{inf}	AUC_{inf} /Dose
C_{max}	Maximum observed concentration	Observed directly from data
C_{max} (dn)	Dose-normalized Cmax	Cmax/Dose
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$	Terminal elimination half-life	Loge(2)/kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL	Clearance	Dose/ AUC_{inf} for cycle 1; Dose/ AUC_{τ} for cycle 4
V_{ss}	Volume of distribution at steady state	CL×MRT
Vz	Volume of distribution based on the terminal phase	CL/λz
R_{ac}	Observed accumulation ratio	$AUC_{cycle\ 4,\ \tau}$/ $AUC_{cycle\ 1,\ \tau}$

7.4. Biomarker Endpoints

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.

Soluble HER2 data will be summarized with descriptive statistics. CCI [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]

7.5. Covariates

Not applicable.

8. HANDLING OF MISSING VALUES

8.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of onset cannot be prior to day one date). In this case, the date resulting in 0 time duration will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration). This excludes the pharmacokinetic, ECG, and pharmacodynamic analyses, which will only use the actual date collected or if date not available deem the data missing.

8.2. Efficacy Analysis

Censoring rules for time-to-event endpoints are detailed in Section 11.2 Appendix 2.

8.3. Pharmacokinetics

Concentrations below the limit of quantification

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

Deviations, missing concentrations and anomalous values

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

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters.

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

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

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

QTc

For the QTc analyses, no values will be imputed for missing data.

Pharmacodynamic parameters

Missing data for the pharmacodynamic parameters will be treated as such and no imputed values will be derived.

9. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

9.1. Statistical Methods

No formal hypothesis testing will be performed in this exploratory study.

Analyses of Time-to-Event Endpoints

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint (Brookmeyer and Crowley, 1982) will be provided.

Analyses of Binary Endpoint

The rates of binary endpoints will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method.

Analyses of Continuous Data

Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints.

9.2. Statistical Analyses

9.2.1. Safety Analyses

Dose Limiting Toxicity

Dose Limiting Toxicity (DLT) is the primary endpoint in Part 1 of the study, which will be summarized by dose level using the Per Protocol Analysis Set for patients in the dose escalation portion of the study. A listing of the DLTs will also be provided.

Adverse Events

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 Adverse Events. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized

according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). The Safety Analysis Set will be used.

Laboratory Tests Abnormalities

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

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

Vital Signs

Vital signs data will be presented as summaries for change from baseline and as categorical summaries for absolute value, decrease and increase from baseline. Absolute values will also be summarized by cycle/day and dose combinations.

9.2.2. 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.

Summary tables of best Overall Response Rate will be provided by tumor type (GC and BC) and dose for Part 1A, and will be provided by patient population and dose (3 mg and 4 mg) for Part 2. Time to event endpoints such as PFS, TTP and DR will also be summarized, but the cohorts could be combined to ensure sufficient sample size with meaningful interpretation.

Efficacy listings will be provided that include best response, first CR/PR date, last date with CR or PR, most recent date without progression, progression date, death date, date of first response and last tumor assessment date, etc.

The following table provides an overview of the efficacy analysis.

Endpoint	Analysis Set	Statistical Method	Model/Covariates/Strata	Missing Data
Overall response	mITT	Exact CI	See aforementioned summary descriptions on data pooling across dose and tumor type	Observed case
Progression Free Survival (PFS)	Full Analysis Set	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 3
Time to Progression (TTP)	Full Analysis Set	Kaplan-Meier	See aforementioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 3
Duration of Response (DOR)	mITT	Kaplan-Meier	See aformentioned summary descriptions on data pooling across dose and tumor type	Censored per Appendix 3

9.2.3. Pharmacokinetics Analyses

Pharmacokinetic Parameters

To assess the pharmacokinetics of PF-06804103 (ADC), total antibody and unconjugated payload, the PK parameters detailed in Section 7.3 will be listed and summarized for subjects in the PK analysis set (as defined in Section 6.5). Missing values will be handled as detailed in Section 8. Each PK parameter will be summarized by dose and cycle and will include the set of summary statistics as specified in the table below:

Parameter	Summary statistics
AUC_{last}, AUCinf AUCinf(dn) AUC_{τ}, AUC_{τ} (dn)Cmax Cmax(dn) CL, VZ, Vss, Rac	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
$T_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum
T_{max}	N, median, minimum, maximum

There will be 1 summary table presenting all PK parameters. This will include data from all cohorts and will be summarized by dose group and cycle.

To assess the relationship between the PK parameters and dose, dose normalized AUC_{inf}, AUC_{last}, AUC_{τ}, and C_{max} will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg/kg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented are presented on the plot.

Pharmacokinetic Concentrations

To assess the PK profile of PF-06804103 (ADC), total antibody and unconjugated payload, PK concentrations will be listed, summarized and plotted for subjects in the PK analysis set (as defined in Section 6.5), where missing and BLQ values will be handled as detailed in Section 8.3.

Presentations for PF-06804103 (ADC), total antibody and unconjugated payload will include:

- a listing of all concentrations sorted by dose, subject id, day and nominal time post dose. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.
- a summary of concentrations by dose, day and nominal time post dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv) and the number of concentrations above the lower limit of quantification.
- a plot of mean concentrations against nominal time postdose by dose (based on the summary of concentrations by dose and time postdose), preferably with all doses also on the same graph.
- a plot of median concentrations against nominal time postdose by dose (based on the summary of concentrations by dose and time postdose), preferably with all doses also on the same graph.
- a log-linear plot of mean concentrations against nominal time postdose by dose (on the same plot), preferably with all doses also on the same graph.
- a log-linear plot of median concentrations against nominal time postdose by dose (on the same plot), preferably with all doses also on the same graph.
- plots (linear and log scale) of individual concentrations against actual time postdose.

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PK concentration is quantifiable in the matrix.

In addition to the above, a median plot (linear and log scale) of the predose concentrations at each cycle against day will be provided for each dose, on the same plot, in order to assess the attainment of steady-state. Individual subject profiles will also be plotted.

For summary statistics and mean/median plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

Population Pharmacokinetic Analysis or PK/PD Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using compartmental or mixed-effect modeling approaches and may also be pooled with other study results. PK/PD modeling may be attempted to investigate any causal relationship between PF-06804103 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.2.4. Biomarker Analyses

For biomarker biopsy samples and blood samples, appropriate summary statistics at screening and post-treatment will be provided; these may include the mean and standard deviation, median, and minimum/maximum levels of biomarker measures or frequency statistics, as appropriate. All summaries will be provided separately for each dosing cohort. For the expansion cohort, summaries will be provided overall and by eachcohort. Summaries will be provided separately for each biomarker type. Graphical methods may be displayed, as appropriate. The appropriate Biomarker Analysis Set will be used.

Other Variables: Immunogenicity Analysis

For the immunogenicity data, a listing, sorted by subject and study day, of the result of ADA screening (positive/negative [<1:negative]), the specificity, and titer will be listed. The percentage of patients with positive ADA and NAb each will be summarized by dose level (Part 1) or by treatment arms (Part 2). 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 and clinical response including PD markers, safety/tolerability and efficacy of PF-06804103 will be explored, if data is warranted.

9.2.5. Standard Analyses

Study Conduct and Patient Disposition

An accounting of the study patients will be tabulated. The subject evaluation groups will be listed. The Full Analysis Set will be used.

Patient discontinuation from treatment and study will be tabulated and listed separately with their reason for discontinuation. The Safety Analysis Set will be used.

Baseline Characteristics

Baseline characteristics such as demographics, prior medication, medical history, ECOG performance status, HER2 status, and primary diagnosis will be tabulated and listed. For

ECOG performance status a shift table (worst post-baseline vs baseline may be produced). The Safety Analysis Set will be used.

Treatment Administration/Compliance

Listings and tables by dose level will be provided. Cycle length is 21 days for monotherapy and 28 days for combination therapy. Day 1 of a cycle is the first date of dose within that cycle. The safety analysis set will be used.

Dose modifications may occur in the following ways:

- Cycle delay—Day 1 of current cycle starts later than 21(+4) days for monotherapy and 28 (+4) days for combination therapy from Day 1 of the previous cycle (only applies to cycle 2 and above);

- Cycle skip (dose delay of greater than 1 cycle)—Day 1 of current cycle starts later than 42 days for monotherapy and 56 days for combination therapy from Day 1 of the previous cycle (only applies to cycle 2 and above). For example, After cycle 1 ended for a patient in Part 1A, a new cycle didn't start until 42 days after cycle 1 day 1, the newly started cycle will be considered as cycle 3, and cycle 2 is considered skipped for this patient.

- Dose reduction—A decrease in the administered total daily dose (non-zero) compared to the planned total daily dose upon enrollment. If in the CRF the prescribed dose unit is mg/kg, but the actual dose is in mg the actual dose mg/kg should be calculated considering the body weight of the patient at that visit if the patient experiences more than 10% change in body weight. To account for the measurement error in IV dosing, only more than 10% above dose reduction from the planned dose for the actual dose will be considered. Occasionally, if sites recalculate doses as per their local standard procedures, such changes will also be documented and used in this analysis.

Intra-patient dose escalation is not allowed in this study. The following will be summarized for each dose level in Part 1 and Part 2, respectively:

- Number of subjects per dose level
- Median and range of number of cycles started per subject
- Number (%) of subjects with cycle delays and cycle skips
-
- Number (%) of subjects with dose reductions
- Number (%) of each reason (AE vs. Other) for cycle delays, cycle skip and dose reductions
- Duration of treatment (median, range)
- Number of cycles before 1st delay (median, range)
- Number of cycles before 1st dose reduction (median, range)
- Number of cycles before 1st dose interruption (median, range)

Listings by patient (ordered by dose level): start date and stop date of each dosing period within each cycle (including records with 0mg), administered total daily dose for each period, any missed doses with unknown dates (yes/no), number of missed doses with unknown dates, reason for any dosing changes will be provided.

Listings by subject and each cycle (ordered by dose level): cycle length, total planned dose, administered total dose, percentage of planned dose, dose delay (yes/no), dose reduction (yes/no), and dose interruption (yes/no) will be provided.

Prior, Concomitant, and Further Therapies

Prior, concomitant, and further therapies (drug and non-drug treatments) will be coded by the World Health Organization (WHO) medical dictionary. Listings of prior, concomitant, and further therapies will be provided.

10. REFERENCES

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11. APPENDICES

11.1. APPENDIX 1: RECIST 1.1 TUMOR ASSESSMENT CRITERIA

Adapted from E.A. Eisenhauer, P. Therasseb, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below:

Measurable Lesions

Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-measurable Lesions

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥ 10 but < 15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥ 15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- **Complete Response (CR):** disappearance of all target lesions.
- **Partial Response (PR): at** least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.
- **Stable Disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

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

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

- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG-PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up

- No FDG-PET at baseline and a positive FDG-PET at follow- up: if the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Determination of Overall Response by the RECIST 1.1 Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 11.1.1.

Table 11.1.1: Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New Lesions	Overall response
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	SD
Indeterminate or missing	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease,			
PD = progressive disease, and NE = Indeterminate			

Best overall response

The best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 11.1.2.

Table 11.1.2: Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = indeterminate.		

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'Global

deterioration of health status'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

11.2. APPENDIX 2: CATEGORICAL CLASSES FOR ECG AND VITAL SIGNS

Categories for QTc

QTcF (ms)	max. ≤ 450	450< max. ≤480	480< max.≤500	max. >500
QTcF (ms) increase from baseline	max. < 30	30≤ max. <60	max. ≥60	
QTc Interval (ms)	max. ≤ 450	450< max. ≤480	480< max.≤500	max. >500
QTc Interval increase from baseline	max. < 30	30≤ max. <60	max. ≥60	

Categories for PR and QRS

PR (ms)	max ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max ≥200	
QRS (ms) increase from baseline	Baseline >100 and max. ≥25% increase	Baseline ≤100 and max. ≥50% increase

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfil these criteria are to be listed in the study report.

11.3. APPENDIX 3: CENSORING DETAILS

Table 11.3.1: Progression Free Survival and Duration of Response

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessment/'start date'	Event after missing or inadequate assessments [a]
4	No event and [withdrawal of consent date ≥ 'start date' OR End of study (EOS) = Patient refused further FU]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any EPOCH after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	Discontinued Due to Adverse Event	Discontinued Due to Adverse Event
8	COMPLETED in Follow-up disposition page.	Completed without an event
9	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

a 2 or more missing or inadequate post-baseline tumor assessments.

Table 11.3.2: TTP Outcome and Event Dates

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment	'start date'	Censored
PD - after at most 1 missing or inadequate post-baseline tumor assessment, or - ≤ *xx weeks* after 'start date'	Date of PD	Event
PD - after 2 or more missing or inadequate tumor assessments[a]	Date of last adequate tumor assessment[a] documenting no PD prior to new anticancer therapy or missed tumor assessments.	Censored
No PD		
New anticancer therapy given prior to PD		
Death due to any cause		

a. If there are no adequate post-baseline assessments prior to the PD, then the time without adequate assessment should be measured from the 'start date'; if the criteria were met, the censoring will be on the 'start date'.
Note: usually xx is 2 times the length of the tumor assessment interval. If no adequate tumor assessment within *xx weeks* after 'start date' then censor at 'start date'.
TTP = time to progression; PD = progressive disease.

Reasons for censoring should be summarized according to the categories in Table 11.3.3 (could be modified as relevant for each trial) following the hierarchy shown.

Table 11.3.3 TTP Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessment/'start date'	Event after missing or inadequate assessments [a]
4	No event and [withdrawal of consent date ≥ 'start date' OR End of study (EOS) = Patient refused further FU]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any EPOCH after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	Discontinued Due to Adverse Event	Discontinued Due to Adverse Event
8	COMPLETED in Follow-up disposition page.	Completed without an event
9	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

a. 2 or more missing or inadequate post-baseline tumor assessments.
TTP = time to progression; PD = progressive disease; EOS = end of study; FU = follow-up.

11.4. APPENDIX 4: LIST OF ABBREVIATIONS

The following is a list of abbreviations that may be used in the SAP.

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

Abbreviation	Term
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
DMC	data monitoring committee
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
ERBB2	
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

Abbreviation	Term
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-ToTtreat
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

Abbreviation	Term
PD	pharmacodynamics
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
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
TCR/ TCRβ	T cell receptoire/T cell receptor
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