Protocol C3441030

A PHASE 1 STUDY OF THE SAFETY, PHARMACOKINETICS AND ANTI-TUMOR ACTIVITY OF TALAZOPARIB, POLY (ADP-RIBOSE) POLYMERASE (PARP) INHIBITOR, IN JAPANESE PATIENTS WITH ADVANCED SOLID TUMORS

Statistical Analysis Plan
(SAP)

Version: **2**

Date: 15 APR 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 27 DEC 2018	1 12 SEP 2017	N/A	N/A

2
15 APR 2021
	2
	28 FEB 2019
		The expansion part was added to evaluate the efficacy, the safety and PK at RP2D of single agent talazoparib in Japanese patients with gBRCA mutated advanced/metastatic breast cancer.	Most of the sections were updated and modified to reflect the addition of the expansion part.
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			In addition, administrative changes were made throughout the SAP associated with the protocol amendment.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3441030. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Talazoparib (PF-06944076 also known as MDV3800 or BMN 673) is a potent, orally bioavailable, small molecule PARP inhibitor in development for the treatment of a variety of human cancers. Talazoparib is cytotoxic to human cancer cell lines harboring gene mutations that compromise DNA repair, an effect referred to as synthetic lethality.

As there was no clinical experience with talazoparib in Japanese patients at the time of study initiation, the current Phase 1 study was initially designed to evaluate the safety, tolerability, preliminary efficacy, and pharmacokinetic (PK) profile of talazoparib as a single agent in Japanese patients with advanced solid tumors. This part is called the dose escalation part.

In the global phase 1 (PRP-001), the MTD and recommended Phase 2 dose (RP2D) as a single-agent was investigated using dose escalation scheme starting from 0.025 mg/day up to 1.1 mg/day. Total of 3 Dose-Limiting Toxicities (DLTs) in Cycle 1 were observed at dose level of 0.9 mg/day (n=1, Grade 3 thrombocytepenia) and 1.1 mg/day (n=2, Grade 3 and 4 thrombocytopenia) when administered continuously with the cycle length of 28 days. The MTD/RP2D was determined as 1.0 mg/day. Based on these results, the starting dose selected in this study is 0.75 mg/day where no DLT was observed and one level lower than the MTD/RP2D. Talazoparib will be administered once daily in continuous dosing regimen with the treatment cycle of 28 days.

The dose escalation part of the C3441030 study applied modified 3+3 dose escalation scheme to identify the RP2D in Japanese patients. The dose was escalated to the next dose level (1.0 mg/day) according to the pre-defined dose escalation scheme and based on the incidence of DLTs at the intial dose level (0.75 mg/day). However, the highest dose used in the study was 1.0 mg/day. The dose over the MTD determined in Study PRP-001 was be explored. The study also includes Lead-in PK period. A single dose of talazoparib was administered 7 days prior to Cycle1 Day1 and multiple PK samples were collected.

As of 24 January 2019, a total of 9 patients were enrolled in the dose escalation part of the C3441030 study. DLT were not reported in any patients receiving 0.75 mg/day (n=3) or 1.0 mg/day (n=6). Therefore, the RP2D of single-agent talazoparib was determined to be 1.0 mg/day in Japanese patients with advanced solid tumors. Overall the safety profile in the dose escalation part was similar to the adverse events (AEs) observed in global studies of talazoparib. Most common AEs of single-agent talazoparib in Japanese patients were hematological toxicities and hepatotoxicities. Based on the preliminary PK analysis results (n=3 each in 0.75 and 1.0 mg/day), the PK profile of single-agent talazoparib in Japanese patients was comparable with that in Western population. These data also supported RP2D in Japanese patients.

Following on the encouraging results of EMBRACA and determination of RP2D in Japanese patients, the C3441030 study was expanded to further evaluate efficacy, safety and PK at RP2D in Japanese patients with gBRCAm HER2-negative locally advanced or metastatic breast cancer in protocol amendment 2.

2.1. Study Objectives, Endpoints, and Estimands

Study Objectives and Endpoints for Dose Escalation part (Solid Tumor)**Primary Objective(s):**	**Primary Endpoint(s):**

• To assess safety and tolerability at increasing dose levels of talazoparib in successive cohorts of patients with solid tumors in order to select the RP2D in Japanese.	• First-cycle DLTs.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the overall safety profile.	• Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to talazoparib. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing. • Vital Signs.

• To characterize the single and steady-state pharmacokinetics (PK) of single-agent talazoparib	• Pharmacokinetic parameters of talazoparib:
	  • Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and V_z/F and $t_{1/2}$, and AUC_{inf} as data permit.
	  • Multiple Dose (MD) (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, C_{min}, $AUC_{ss,\tau}$, CL/F, R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$) and R_{ss} ($AUC_{ss,\tau}$ /$AUC_{sd,inf}$) as data permit.

• To assess preliminary evidence of anti-tumor activity of single agent talazoparib.	• Objective response (OR), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 • Time-to-event endpoints: eg, DoR and PFS if applicable
CCI [redacted]	

Study Objectives and Endpoints for Expansion part (gBRCAm breast cancer)

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the anti-tumor activity of single agent talazoparib in Japanese patients with gBRCAm HER2-negative locally advanced or metastatic breast cancer.	• Confirmed objective response (OR) as assessed using RECIST version 1.1 by Investigator Assessment.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To further evaluate anti-tumor activity.	• OR as assessed using RECIST version 1.1 by Blinded Independent Central Review (BICR). • Disease Control defined as patients with a confirmed complete response (CR), confirmed partial response (PR) and stable disease (SD) at 16 and 24 weeks. • Time to event endpoints: Time-to-tumor response (TTR),

	DoR, PFS, and OS.
• To evaluate the overall safety profile of talazoparib.	• AEs including laboratory abnormalities as characterized by type, frequency, severity (as graded by the NCI CTCAE, version 4.03), timing, seriousness, and relationship to talazoparib.
• To characterize the PK of single-agent talazoparib.	• Trough concentrations of talazoparib.

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2.1.1. Primary Estimand

The primary estimand of this study is a composite estimand (accounting for both treatment adherence and response), defined according to the primary objective and in alignment with the primary endpoint. It includes the following 4 attributes:

Dose Escalation part

- Population: Japanese patients with advanced solid tumors, as defined by the inclusion and exclusion criteria, and who do not have major treatment deviations during the first cycle. One of the non-negligible major treatment deviations is low adherence defined as less than 75% of the planned first cycle dose of study treatment due to toxicity that is not attributable to study treatment. The details of analysis set, Per Protocol, is defined in Section 4.

- Variable: Binomial DLT occurrence within the first cycle. The DLTs are defined in Section 3.1.1.

- Intercurrent event(s): The intercurrent event is captured through the variable definition.

- Population-level summary: Percentage of patients who experienced DLT within the first cycle.

Expansion part

- Population: Japanese patients with gBRCAm HER2-negative locally advanced or metastatic breast cancer, as defined by the inclusion and exclusion criteria, and who received at least 1 dose of study drug without regard to tolerability or duration of treatment. The details of analysis set, Full analysis set, is defined in Section 4.

- Variable: Confirmed objective response defined as CR or PR according to RECIST v1.1 based on investigator assessment.
- Intercurrent event(s): The intercurrent event is captured through the variable definition.
- Population-level summary: Percentage of patients who experienced confirmed objective response.

2.1.2. Secondary Estimand

Not applicable

2.1.3. Additional Estimand

Not applicable

2.2. Study Design

This is a Phase 1 study which consists of 2 parts; Dose Escalation part and Expansion part.

The dose escalation part is open label and evaluates safety, preliminary efficacy and PK of single agent talazoparib in sequential cohorts of adult patients with advanced solid tumors who are resistant to standard therapy or for whom no standard therapy is available. Successive cohorts of patients received escalating doses of talazoparib on an outpatient basis starting from 0.75 mg/day. This part evaluated 2 dose levels; 0.75 mg and 1.0 mg. To understand the single dose safety and single dose PK assessments of talazoparib, a lead-in period preceding the continuous daily doses have been included in the dose escalation part. In the 7-day lead in period, a single lead in dose was given on Day -7. No talazoparib was administered during the interval between the lead-in single dose and Day 1 of the first cycle. Study treatment is given as on outpatient basis, however a patient is required to stay overnight at the study site during any intensive PK collection period (i.e. Day -7 and Day 22 in Cycle 1).

In the dose escalation part, a total of 9 patients were enrolled. No DLTs were observed in any patients receiving 0.75 mg/day (n=3) or 1.0 mg/day (n=6). Therefore enrollment was completed for dose escalation part.

Protocol amendment 2 includes the addition of an expansion part. The expansion part is an open-label, multicenter, efficacy, safety and PK study of single-agent talazoparib at RP2D determined in the dose escalation part in adult patients with locally advanced or metastatic breast cancer who have deleterious or suspected deleterious germline BRCA1 or BRCA2

mutations. The patients in the expansion part will receive 1.0 mg/day of talazoparib which was RP2D identified in the dose escalation part of the C3441030 study. The expansion part will include Blinded Independent Central Review (BICR) assessment for the efficacy evaluation. All radiographic images taken during the study must be available and be submitted for central review.

In the expansion part, a minimum of 17 patients will be enrolled evaluable for the primary endpoint.

In all study parts, treatment with talazoparib will continue until either disease progression, unacceptable toxicity or withdrawal of consent.

2.2.1. Starting Dose

The starting dose was 0.75 mg given once daily in 28-day cycles in dose escalation part.

The starting dose in expansion part will be 1.0 mg/day. In patients with moderate renal impairment (creatinine clearance 30-59 mL/min), the starting dose will be reduced 1 dose level.

2.2.2. Criteria for Dose Escalation (Dose Escalation part only)

A modified 3+3 dose escalation scheme will be used.

Two dose levels (0.75 mg/day and 1.0 mg/day) will be evaluated in the dose escalation part. Up to 3 patients in a cohort may be enrolled simultaneously; occasionally, due to logistical/clinical reasons, more than 3 but no more than 9 patients may be enrolled at each dose level. Initially, 3 patients will receive 0.75 mg/day. If no DLT is observed in the initial 3 patients at 0.75 mg/day, the next dose level at 1.0 mg/day will be opened. If a DLT is observed in 1 or 2 of the initial 3 dosed patients, 3 additional patients up to a total of 6 patients will be enrolled and receive 0.75 mg/day. If 1 of 6 patients experience a DLT at 0.75 mg/day, the dose will be escalated to 1.0 mg/day. In case 2 of 6 dosed patients experience a DLT, 3 additional patients up to a total of 9 patients will be enrolled and receive 0.75 mg/day if deemed necessary in the opinion of the sponsor and the investigators. For the case where 2 of 6 dosed patients experience a DLT but additional 3 patients will not be enrolled, RP2D will not be determined in the current study design. Dose escalation will complete if a DLT is observed in 2 of 9 patients and the RP2D will be declared at 0.75 mg/day. If ≥3 patients experience a DLT, no further patients will be dosed at that dose or higher.

Following dose escalation, 3 patients will receive 1.0 mg/day. If a DLT is observed in >1 of the initial 3 dosed patients, 0.75 mg/day may be evaluated and the above dose escalation schema will be followed. If a DLT is observed in ≤1 of initial 3 patients at 1.0 mg, 3 additional patients up to a total of 6 patients will be enrolled and receive 1.0 mg/day. In case a DLT is observed in 2 of 6 dosed patients, 3 additional patients up to a total of 9 patients will be enrolled and receive 1.0 mg/day if deemed necessary in the opinion of the sponsor and the investigators. Dose escalation will complete if a DLT is observed in ≤1 of 6 patients or in 2 of 9 patients and the RP2D will be declared at 1.0 mg/day. If a DLT is observed in >2 of 9 (or 2 of 6 if 3 additional patients will not be enrolled) patients, the RP2D may be declared at 0.75 mg/day if 6 patients are evaluated with ≤1 DLT at 0.75 mg/day, or additional patients will be enrolled at 0.75 mg/day to declare the RP2D.

Patients not meeting the criteria for inclusion in the Per Protocol Analysis set defined in Section 4 (i.e., not evaluable for assessment of DLT) will be replaced. The safety

information obtained from the patients who are excluded from the Per Protocol Analysis set may be used for determination of dose escalation.

Subsequent dose levels may not be used (except within a patient, see below) until all patients entered at the current dose level have been dosed and observed for at least one complete cycle, and the number of DLTs among those patients in their first cycle has been determined.

Intrapatient dose escalation may be permitted in the C3441030 study. A patient may have his/her dose-escalated to the next highest dose level if all of the following conditions are satisfied:

- Cycle 1 was completed without any DLT;
- His/her maximum talazoparib-related toxicity during prior cycles of therapy was Grade ≤2;
- Minimum 3 patients at the highest dose level have completed Cycle 1 with talazoparib without having DLT or 1 out of 6 or 2 out of 9;
- The decision to increase the dose has been approved by discussion with both the investigator and the sponsor. A patient whose dose has been escalated will not contribute to the assessment of the number of DLTs at the escalated dose level.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint of dose escalation part is the first-cycle DLTs as defined in Section 3.1.1. The primary endpoint of expansin part is confirmed OR as assessed using RECIST version 1.1 by Investigator Assessment as defined in Section 3.2.3.

3.1.1. DLT Definition (Dose Escalation part only)

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 including the PK lead-in period which are attributable to talazoparib will be classified as DLTs:

Hematologic:

- Grade 4 neutropenia lasting >7 days;
- Febrile neutropenia (defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3 °C or a sustained temperature of ≥38°C for more than 1 hour);
- Grade ≥3 neutropenic infection (defined as ANC < 1000/mm^3 or <1.0 x 10^9/L and Grade >3 infection);

- Grade ≥3 thrombocytopenia associated with ≥ Grade 2 hemorrhage or requiring transfusion;
- Grade 4 thrombocytopenia;
- Grade 4 anemia;
- Grade 3 anemia requiring transfusion;
- If daily dosing is interrupted for 7 or more total days in the first cycle for Grade 3 neutropenia or Grade 3 thrombocytopenia.

Non-hematologic:

Any Grade ≥3 AE, except:

- Non-clinically significant Grade ≥3 laboratory abnormalities;
- Non-hematologic Grade ≥3 AE deemed not clinically significant;
- Grade ≥3 nausea, vomiting and diarrhea that responds to medical intervention within 72 hours;
- Grade ≥3 fatigue that improves to Grade ≤2 within 7 days;

Liver toxicity:

- Alanine or aspartate aminotransferase (ALT or AST) > 5×upper limit of normal (ULN) (a lower threshold should be considered if the ALT/AST abnormalities are accompanied with symptoms and signs of hepatitis) AND 2×increases above the baseline values;
- ALT/AST ≥3×ULN concurrent with total bilirubin (TBili) >2×ULN;
- TBili >5×ULN.

General toxicity:

- Failure to deliver 75% of doses due to toxicities attributable to talazoparib.

3.2. Secondary Endpoint(s)

3.2.1. Safety Endpoints

Secondary safety endpoints are described in Section 3.5.

3.2.2. Pharmacokinetic Endpoints

- PK parameters of talazoparib single dose if data permit (Table 2).

Table 2. Pharmacokinetic Parameters of Talazoparib Single Dose

Parameter	Definition	Method of Determination
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{τ}	Area under the plasma concentration-time profile from time zero to time tau (τ), where τ = 24 hours for QD dosing	Linear/Log trapezoidal method
CL/F[a]	Apparent clearance	Dose / AUC_{inf}
V_z/F[a]	Apparent volume of distribution	Dose / ($AUC_{inf} \cdot k_{el}$) where k_{el} 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 were used in the regression.
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$,
AUC_{inf}[a]	Area under the plasma concentration-time profile from time zero extrapolated to infinity	AUC_{last} + (C_{last}^*/ kel), where C_{last}^* is the estimated concentration at the time of the last quantifiable concentration.
AUC_{inf}(dn)[a]	Dose normalized AUC_{inf}	AUC_{inf} / Dose
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last} / Dose
C_{max}(dn)	Dose normalized C_{max}	C_{max} / Dose

[a] If data permit

- PK parameters of talazoparib multiple dose assuming that steady state is achieved if data permit (Table 3).

Table 3. Pharmacokinetic Parameters of Talazoparib Multiple Dose

Parameter	Definition	Method of Determination
$C_{ss,max}$	Maximum observed plasma concentration (at steady state)	Observed directly from data
C_{min}	Predose concentration during multiple dosing	Observed directly from data
$T_{ss,max}$	Time for C_{max} (at steady state)	Observed directly from data as time of first occurrence
$AUC_{ss,\tau}$	Area under the plasma concentration-time profile from time zero to time tau (τ), where τ = 24 hours for QD dosing (at steady state)	Linear/Log trapezoidal method
CL/F_{ss}	Apparent clearance (at steady state)	Dose / $AUC_{ss,\tau}$
R_{ac}	Accumulation Ratio	$AUC_{ss,\tau}$ /$AUC_{sd,\tau}$
R_{ss}[a]	Linearity Ratio	$AUC_{ss,\tau}$ /$AUC_{sd,inf}$
AUC_{τ}(dn)	Dose normalized AUC_{τ}	AUC_{τ} / Dose

Table 3. Pharmacokinetic Parameters of Talazoparib Multiple Dose

Parameter	Definition	Method of Determination
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last} / Dose
C_{max}(dn)	Dose normalized C_{max}	$C_{ss,max}$ / Dose
C_{min}(dn)	Dose normalized C_{min}	C_{min} / Dose

[a] If data permit

3.2.3. Efficacy Endpoints

3.2.3.1. Tumor Assessment

Objective response status will be assessed by investigators at each assessment and recorded on the CRF using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 defined by Eisenhauer et al (2009)[1].

3.2.3.1.1. Categorizing Lesion 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 Lesions

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

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

Normal Sites

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

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

Recording Tumor Assessments

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

Target Lesions

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

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

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

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

Non-target Lesions

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 (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

3.2.3.1.2. Objective Response Status at Each Assessment

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 Lesions

- 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 Disease (SD): 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.

- 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 (e.g., 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 Lesions

- 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.

Objective Response Status

Assessment is based on the target and non-target lesions response as described in Table 4 and Table 5.

Table 4. Objective Response Status at Each Assessment for Patients with Target Lesions at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD or Indeterminate	No	PR
PR	Non-PD* or Indeterminate	No	PR
SD	Non-PD* or Indeterminate	No	SD
Indeterminate	Non-PD*	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Table 4. Objective Response Status at Each Assessment for Patients with Target Lesions at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective Status
Any	Any	Yes**	PD

* Non-PD includes CR and Non-CR/Non-PD
** New lesions must be unequivocal

Table 5. Objective Response Status at Each Assessment for Patients with Non-target Lesions Only at Baseline

Non-target Lesions	New Lesions	Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
PD	Yes or No	PD
Any	Yes*	PD

* New lesions must be unequivocal

Date of Response

If there are multiple scan dates associated with a tumor evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the earliest scan date associated with the evaluation will be used as the date of the assessment.

Time to Response (TTR)

For patients with an Objective Response (PR or CR), TTR is defined as the time from the first dose date to date of first documentation of Objective Response.

3.2.3.2. Best Overall Response (Confirmed Response)

The best overall response is the best response recorded from start date until disease progression or start of new anti-cancer therapy. The best overall response will be programmatically derived based on the investigator assessments of objective response status.

CR: Two objective statuses of CR a minimum of four weeks apart documented before progression and start of new anti-cancer therapy.

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

SD: At least one objective status of stable or better documented at least 6 weeks after start date and before progression and the start of new anti-cancer therapy but not qualifying as CR or PR.

PD: Progression documented within 16 weeks after start date and not qualifying as CR, PR or SD.

Not Evaluable (NE): All other cases. Note that reasons for NE will be summarized and the following reasons could be used:

- Early death (Note: death prior to 6 weeks after start date)
- No post-baseline assessments
- All post-baseline assessments have overall response Indeterminate
- New anti-cancer therapy started before first post-baseline assessment
- SD too early (<6 weeks after start date)
- PD too late (>16 weeks after start date)

Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD too early'.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR–SD–PR is considered a confirmed PR. A sequence of PR–SD–SD–PD would be a best response of SD if the window for SD definition has been met.

The overall response rate (ORR) is defined as the percentage of patients with a best overall response of CR or PR.

The disease control rate (DCR) is defined as the percentage of patients with a best overall response of CR, PR, SD or Non-CR/Non-PD.

3.2.3.3. Best Overall Response (Unconfirmed Response)

Unconfirmed CR (uCR): One objective status of CR documented before progression or start of new anti-cancer therapy.

Unconfirmed PR (uPR): One objective status of PR documented before progression and start of new anti-cancer therapy, but not qualifying as uCR.

SD: At least one objective status of SD or better documented at least 6 weeks after start date and before progression and the start of new anti-cancer therapy but not qualifying as uCR or uPR.

PD: Progression documented within 16 weeks after start date and not qualifying as uCR, uPR or SD.

Not Evaluable (NE): All other cases. Note that reasons for NE will be summarized and the following reasons could be used:

- Early death (Note: death prior to 6 weeks after start date)
- No post-baseline assessments
- All post-baseline assessments have overall response Indeterminate
- New anti-cancer therapy started before first post-baseline assessment
- SD too early (<6 weeks after start date)
- PD too late (>16 weeks after start date)

Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD too early'.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds.

The unconfirmed overall response rate (uORR) is defined as the percentage of patients with a best overall response of uCR or uPR.

The unconfirmed disease control rate (uDCR) is defined as the percentage of patients with a best overall response of uCR, uPR, SD or Non-CR/Non-PD.

3.2.3.4. Percent Change from Baseline in Sum of Diameters for Target Lesions

Percent change from baseline in sum of diameters for target lesions at each assessment based on investigator assessment will be derived. Within all post-baseline assessements, the best (reduced) percent change from baseline in sum of diameters for target lesions will also be derived.

3.2.3.5. Progression Free Survival (PFS)

PFS is defined as the time from the first dose date to date of first documentation of PD or death due to any cause.

PD or death within 16 weeks of the last adequate tumor assessment or within 16 weeks after the start date will be counted as an event according to the tumor assessment date or date of death, as appropriate.

Censoring: Patients without an event or with an event more than 16 weeks after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment that documented no progression. In addition, if a new anti-cancer therapy is

started prior to an event, the patient will be censored on the date of the last adequate tumor assessment that documented no progression prior to the start of the new anti-cancer therapy.

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, Non-CR/Non-PD, or PD can be determined. Time points where the response is Indeterminate or no assessment was performed will not be used for determining the censoring date.

Patients with no baseline tumor assessment (including patients with an inadequate baseline assessment) or with no adequate post-baseline tumor assessments within 16 weeks after the start date will be censored on the start date, unless the patient dies within 16 weeks of the start date, in which case, death will be an event on date of death.

Events and censoring rules are summarized in Table 6.

Table 6. PFS Outcome and Event Dates

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment	Start date [a]	Censored [a]
PD or death ≤16 weeks after last adequate tumor assessment or ≤16 weeks after start date	Date of PD or death	Event
PD or death >16 weeks after the last adequate tumor assessment [b]	Date of last adequate tumor assessment [b] documenting no PD prior to new anti-cancer therapy or missed assessments	Censored
No PD		
New anti-cancer therapy given		

a. If the patient dies ≤16 weeks after start date, the death is an event with date on death date.
b. If there are no adequate post-baseline assessments prior to the PD or death, 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.

Reasons for censoring should be summarized according to the categories in Table 7 following the hierarchy shown.

Table 7. PFS 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 more than 8 weeks from last adequate post-baseline tumor assessment/start date	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ start date OR End of study (EOS) = Subject refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any	Lost to follow-up

Table 7. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
	disposition page	
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	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

a. more than 16 weeks after last adequate tumor assessment.

3.2.3.6. Duration of Response (DoR)

For patients with an objective response, DoR is the time from first documentation of PR or CR to date of first documentation of PD or death due to any cause.

Censoring: Same as censoring for the definition of PFS.

3.2.3.7. Overall Survival (OS)

OS is defined as the time from the first dose date to date of death due to any cause.

Censoring: Patients last known to be alive are censored at date of last contact.

The date of last contact will be derived for patients not known to have died at the analysis data cutoff date using the latest complete date (non-imputed) among the following:

- All patient assessment dates (e.g., blood draws [laboratory, PK], vital signs, performance status, ECG, tumor assessments, concomitant radiation, surgery)
- Start and end dates of follow-up anti-cancer therapies
- AE start and end dates
- Last date of contact where "Subject Remains in Follow-up" collected on the "Survival Follow-up" eCRF (do not use date of survival follow-up assessment unless status is alive)
- Study drug start and end dates
- Randomization date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up or death).

3.2.3.8. Time to Response (TTR)

For patients with an OR (PR or CR), TTR is defined as the time from the first dose date to date of first documentation of OR in expansion part.

CCI

[redacted]

3.4. Baseline Variables

Baseline value will be defined as the value prior to dosing study treatment (either screening or lead-in visit, whichever is closer to the first dose).

Baseline characteristics including demographics, physical measurements, disease history and prior anti-cancer therapies described in Section 6.5.1 will be summarized according to Pfizer Safety Rulebook[2].

3.5. Safety Endpoints

Safety endpoints will be summarized according to Pfizer Safety Rulebook[2].

3.5.1. Adverse Events

An AE is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment, or
- the event was seen prior to the start of treatment but increased in severity during treatment.

The treatment-emergent period is defined as the period of time from the date and time of the first dose of study drug through 30 days after the last dose (permanent discontinuation of study drug) or the day before initiation of a new antineoplastic therapy, whichever occurs first. The treatment-emergent period will be used in the summaries of treatment-emergent adverse events (TEAEs).

Assessment of AEs will include the type, incidence, severity (graded by investigators according to the NCI CTCAE version 4.03), timing, seriousness, and relatedness. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Clustered MedDRA preferred term might be defined by the study team in Pfizer and documented separately from this analysis plan.

3.5.2. Laboratory Data

Laboratory abnormalities will be characterized by type, frequency and severity (graded by the NCI CTCAE, version 4.03), and timing.

Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of NCI CTCAE criteria (e.g. hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 1 will not be derived).

Abnormalities classified according to NCI CTCAE will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g. hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g. hyperkalemia), and vice versa.

For white blood cell (WBC) differential counts (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the NCI CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) × (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased
    - Derived absolute count does not meet Grade 2-4 criteria, and
    - % value < % LLN value, and
    - Derived absolute count $\geq 800/mm^3$
- Neutrophil count decreased
    - Derived absolute count does not meet Grade 2-4 criteria, and
    - % value < % LLN value, and
    - Derived absolute count $\geq 1500/mm^3$

For calcium, NCI CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

- Corrected Calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 – serum Albumin [g/L])

Clinically significant abnormalities will be identified by a comparison against prespecified percentage of the normal range (e.g. >20% above the Upper Limit of Normal or >10% below the Lower Limit of Normal). Different laboratory tests will look for abnormalities above the upper normal range, or below the lower normal range, or both.

3.5.3. Vital Signs

Patients will have assessments to include weight, height, blood pressure (BP) and pulse rate, and Eastern Cooperative Oncology Group (ECOG) performance status. BP and pulse rate to be recorded in sitting position. Height will be measured at baseline only (screening visit). Body Mass Index (BMI) will be derived if weight and height are collected as:

$$BMI(kg/m^2) = \frac{Weight(kg)}{(Height(cm)/100)^2}$$

3.5.4. Electrocardiograms

A single 12-lead electrocardiogram (ECG) will be performed. QT intervals will be corrected for heart rate (HR) (QTc) using Fridericia's and Bazett's correction factors:

- Fridericia's correction: $QTcF = \frac{QT}{\sqrt[3]{60/HR}}$
- Bazett's correction: $QTcB = \frac{QT}{\sqrt{60/HR}}$

If HR are not collected, HR will be derived by RR interval as;

$HR = (60 / RR) \times 1000$

where HR in beats per minute (bpm) and RR interval in milli-seconds. Then QTcF and QTcB will be derived using RR interval.

- Fridericia's correction: $QTcF = \frac{QT}{\sqrt[3]{RR/1000}}$
- Bazett's correction: $QTcB = \frac{QT}{\sqrt{RR/1000}}$

If the QTcF is prolonged (>500 msec, i.e., CTCAE Grade ≥3), 3 consective ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval to confirm presence of QTc prolongation and the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional ECGs may be performed as clinically indicated.

The following ECG tests will be observed or derived. Although there are observed and derived QTcF values, derived QTcF will be primarily used for analysis.

- Observed ECG tests through eCRF
  - RR interval
  - PR interval
  - QRS interval
  - QT interval
  - QTc interval
  - QTcF interval
- Derived ECG tests
  - QTcF interval
  - QTcB interval

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who sign the informed consent document.
Full	All participants assigned to study treatment and who take at least 1 dose of study treatment.
Per Protocol	Per Protocol Analysis Set (PPAS) will be evaluable for RP2D and a subset of the Full Analysis Set (FAS) in dose escalation part only. This set will exclude patients with major treatment deviations in the first cycle; who are not evaluable for the RP2D assessment and will be replaced as needed to permit RP2D estimation. Major treatment deviations include: • Administration of less than 75% of the planned first cycle dose of talazoparib (provided that it is not due to toxicity attributable to talazoparib) • Administration of more than 125% of the planned first cycle dose of talazoparib

Population	Description
Safety	All participants assigned to study treatment and who take at least 1 dose of study treatment.
Pharmacokinetic Parameter	All enrolled participants treated who have sufficient information to estimate at least 1 of the pharmacokinetic parameters of interest in dose escalation part only.
Pharmacokinetic Concentration	All enrolled participants who are treated and have at least 1 analyte concentration.

5. GENERAL METHODOLOGY AND CONVENTIONS

Primary completion date (PCD) will be the date of 24 weeks after Last Subject First Dose (LSFD). Primary analysis up to PCD will follow the official primary database release. Final analysis will follow the official final database release.

5.1. Hypotheses and Decision Rules

There is no formal hypothesis testing planned for this study. In the dose escalation part, the objective is to determine RP2D. The estimated RP2D will be the highest tested dose level with DLT rate less than 33% in at least 6 DLT-evaluable patients in the Per Protocol Analysis Set. In the expansion part, the objective is to estimate ORR. If the lower limit of the two-sided 90% CI of confirmed ORR exceeds 18.4%, observed ORR in physician's choice therapy (PCT) arm in EMBRACA study, it is considered that talazoparib shows clinical meaningful antitumor activity in Japanese patients with gBRCAm locally advanced/metastatic breast cancer.

5.2. General Methods

Unless otherwise specified, analyses and summaries will be presented by starting dose groups and total group as follows. Total group will not be presented if there is only one starting dose group.

- Talazoparib 0.75 mg/day
- Talazoparib 1.0 mg/day
- Total

5.2.1. Analyses for Binary Endpoints

The number and percent will be presented. Unless otherwise specified, the 95% confidence interval (CI) for the percent will also be presented when applicable. The CI will be obtained using exact method (Clopper-Pearson method) based on binomial distribution.

5.2.2. Analyses for Continuous Endpoints

Appropriate descriptive statistics will be presented depending on the distribution. In general, the number, mean, standard deviation will be presented. Other descriptive statistics [e.g.

minimum, 1st , 2nd and 3rd quartiles, maximum, standard error of the mean, coefficient of variation (CV), geometric mean and geometric CV] will also be presented when appropriate.

5.2.3. Analyses for Categorical Endpoints

The number and percent of each category will be presented.

5.2.4. Analyses for Time-to-Event Endpoints

Time-to-event endpoints will be descriptively summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. Confidence intervals for medians and quartiles are based on the Brookmeyer-Crowley method. Confidence intervals for the estimated probability of an event at a particular time point will be generated using the Greenwood formula.

5.3. Methods to Manage Missing Data

5.3.1. Efficacy and Safety Endpoints

In general, missing values will not be imputed for efficacy and safety endpoints except for impuations according to standard algorithms[2] or imputations provided below.

Missing or partial dates will be imputed when date is required for a calculation of duration.

Missing or Partial Death Dates

If there is a record for death, but the date is missing or is partial, it will be imputed based on the last contact date defined in Appendix 1.2.

- If the entire date is missing, the death date will be imputed as the day after the date of last contact.
- If the day or both day and month is missing, the death date will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - 1st day of the month and year of death, if day of death is missing OR
  - January 1st of the year of death, if both the day and month of death are missing.

Date of Last Dose of Study Drug

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no Disposition CRF page and no death date, the patient will be considered to be ongoing and use the cutoff date for the analysis as the last dosing date.

- If the last date of study drug is completely or partially missing and there is EITHER an Disposition (End of Treatment) CRF page OR a death date available (within the data cutoff date), then impute this date as the last dose date:
    - = 31DECYYYY, if only Year is available and Year < Year of min (Disposition date, death date)
    - = Last day of the month, if both Year and Month are available and Year = Year of min (Disposition date, death date) and Month < Month of min (Disposition date, death date)
- = min (Disposition date, death date), for all other cases.

Date of Start of New Anti-cancer Therapy

Incomplete dates for start date of new anti-cancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
    - completely missing then it will be ignored in the imputations below
    - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
    - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For patients who have not discontinued study treatment at the analysis cutoff date, last dose of study treatment is set to the analysis cutoff date is the imputations below
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is:
    - = 31DECYYYY, if only Year is available and Year < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
    - = Last day of the month, if both Year and Month are available and
        - Year = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
        - Month < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

- = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], for all other cases.

Other Missing or Partial Dates

In compliance with the Pfizer Safety Rulebook[2], imputation methods generally apply to partial dates as follows:

- If the day of the month is missing for a start date used in a calculation, the 1st of the month will be used to replace the missing date.
- If both the day and month are missing, the first day of the year is used.
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

These rules are used unless the calculations result in negative time durations (e.g., date of resolution cannot be prior to date of onset). In these case, the resolution and onset dates will be the same and the duration will be set to 1 day.

5.3.2. Pharmacokinetic Endpoints

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 having set concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (i.e., not done) or NS (i.e., no sample);
2. A deviation in sampling time is of sufficient concern (>10% of the nominal time) or a concentration has been flagged anomalous by the pharmacokineticist.

Pharmacokinetic Parameters

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

If a PK parameter cannot be derived from a patient's concentration data due to insufficient sampling, the parameter will be coded as NC (i.e., not calculated). If PK parameter cannot be derived from a patient's concentration data due to discontinuation of treatment, the parameter will be coded as NS (i.e., no sample).

In summary tables, statistics will be calculated by setting NC and NS values to missing; and statistics will be presented for a particular treatment with ≥3 evaluable measurements. For statistical analyses (i.e., analysis of variance), PK parameters coded as NC will also be set to

missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual patient has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately 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.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. First-cycle Dose-Limiting Toxicities (DLTs) in Dose Escalation part

6.1.1.1. Main Analysis

- Estimand strategy: Composite (Section 2.1.1).
- Analysis set: Per Protocol (Section 4).
- Analysis methodology: The number and percentage of patients who experienced DLTs listed in Section 3.1.1 will be presented by each dose group and total group.
- Intercurrent events and missing data: The intercurrent event is captured through the DLTs definition (Section 2.1.1). Missing data is not expected.
- DLTs recorded on the CRF and adverse events constituting DLTs will be listed.

6.1.1.2. Sensitivity/Supplementary Analyses

Since there are no statistical assuptions and missing data is not expected, no sensitivity and supplementary analysis will be conducted.

6.1.2. Confirmed objective response (OR) as assessed using RECIST version 1.1 by Investigator Assessment in Expansion part

6.1.2.1. Main Analysis

- Estimand strategy: Composite (Section 2.1.1).
- Analysis set: Full Analysis Set (Section 4).
- Analysis methodology: The number, percentage and exact two-sided 90% CI of patients who experienced confirmed objective response as assessed using RECIST version 1.1 by Investigator Assessment.
- Intercurrent events and missing data: The intercurrent event is captured through the the variable definition (Section 3.2.3). Missing data is not expected.

6.1.2.2. Sensitivity/Supplementary Analyses

Since there are no statistical assuptions and missing data is not expected, no sensitivity and supplementary analysis will be conducted.

6.2. Secondary Endpoint(s)

Analyses and summaries for secondary safety endpoints are described in Section 6.6.

6.2.1. Pharmacokinetic Endpoints

6.2.1.1. Single-Dose and Steady-State Talazoparib Pharmacokinetic Analysis

Plasma PK parameters and concentrations of talazoparib will be analyzed on PK Parameter Analysis Set and PK Concentration Analysis Set, respectively (Section 4). Missing data will be treated as described in Section 5.3.2.

Dose Escalation part

Plasma PK parameters including the maximum concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration versus time curve (AUC_{last}, AUC_{τ}) and the lowest concentration observed during the dosing interval (C_{min}) for talazoparib will be estimated using noncompartmental analysis. If data permit or if considered appropriate, area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{inf}), terminal phase half-life ($t_{½}$), apparent oral clearance (CL/F), apparent volume of distribution (V_z/F), accumulation ratio (R_{ac}) and linearity ratio (R_{ss}) will be also estimated. The single-dose in lead in phase and steady-state PK parameters on Day 22 in Cycle 1 will be summarized descriptively (n, arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV for PK parameters except T_{max} and $t_{1/2}$, n, median, minimum, maximum for T_{max}, n, arithmetic mean, SD, CV, median, minimum, maximum for $t_{½}$) by dose, cycle and day.

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by analyte where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation (AUC_{extrap}%); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the clinical study report.

For talazoparib concentrations, concentrations will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time. Individual patient, median and mean profiles of the concentration-time data will be plotted by dose, cycle and day (single dose and steady state) using nominal times. Individual, median and mean profiles will be presented on both linear-linear and log-linear scales.

Dose normalized AUC_{inf} (AUC_{τ} at steady state), AUC_{last}, C_{max} and C_{min} (only at steady state) will be plotted against dose by cycle and day. These plots will include individual patient

values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

The observed accumulation ratio and the linearity ratio will be summarized descriptively.

Trough concentrations will be plotted for each dose using a box-whisker plot by cycle and day within cycle.

All the concentration data will be listed but the concentrations deviated more than 10% from the planned time will not be included in summarization.

Expansion part

Trough concentrations (C_{trough}) at steady-state will be summarized descriptively (n, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by cycle and day (if the data permits, by each dose). C_{trough} at steady-state will be plotted for each dose using a box whisker plot by cycle and day. Individual mean C_{trough} values of all cycles will be calculated, and then the geometric mean and geometric %CV will be provided.

C_{trough} at steady-state is defined as the pre-dose concentration that meets the following dose-compliant acceptance criteria:

- Patient must have received 7 consecutive days at the same dose of talazoparib once daily prior to the pre-dose PK sampling.
- PK samples must have been collected 24 hours ±10% after the dose administered the day prior to the pre-dose PK sampling.

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

PK and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between talazoparib exposure [redacted] or significant safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately.

6.2.2. Efficacy Endpoints

6.2.2.1. Objective Response

Objective responses will be analyzed on the Full Analysis Set (Section 4).

Dose Escalation part

The number and percent of the each unconfirmed best overall response and each reason for NE will be presented. The number, percent and its exact 95% CI of the unconfirmed overall response and unconfirmed disease control will be presented, respectively.

The best percent change from baseline in sum of diameters for target lesions based on investigator assessment will be plotted in bar chart sorted in descending order from positive (increased) to negative (decreased).

All tumor measurements and assessments based on investigator assessment will be presented in the form of patient data listings that include, but are not limited to, evaluation date, lesion type, lesion number, disease site, lesion site, lesion assessment and procedure.

All objective tumor assessments based on investigator assessment will be presented in the form of patient data listings that include, but are not limited to, evaluation date, response parameter (e.g. sum of diameters for target, target response, non-target response, new lesion progression, overall response and best overall response) and assessment result.

All derived tumor assessments and responses based on investigator assessment will be listed.

Expansion part

The number and percent of the each confirmed and unconfirmed best overall response and each reason for NE based on investigator assessment and BICR assessment will be presented, respectively. The number, percent and its exact 90% CI of the confirmed and unconfirmed overall response and confirmed and unconfirmed disease control (overall, at 16 weeks and 24 weeks) will be presented, respectively.

The best percent change from baseline in sum of diameters for target lesions based on investigator assessment and BICR assessment will be plotted in bar chart sorted in descending order from positive (increased) to negative (decreased), respectively.

All tumor measurements and assessments based on investigator assessment and BICR assessment will be presented in the form of patient data listings that include, but are not limited to, evaluation date, lesion type, lesion number, disease site, lesion site, lesion assessment and procedure.

All objective tumor assessments based on investigator assessment and BICR assessment will be presented in the form of patient data listings that include, but are not limited to, evaluation date, response parameter (e.g. sum of diameters for target, target response, non-target response, new lesion progression, overall response and best overall response) and assessment result.

All derived tumor assessments and responses based on investigator assessment and BICR assessment will be listed.

6.2.2.2. Time to Response (TTR)

TTR based on investigator assessment and BICR assessment will be analyzed on the patients with confirmed CR or PR in the Full Analysis Set (Section 4) in expansion part.

6.2.2.3. Duration of Response (DoR)

DoR based on investigator assessment and BICR assessment (expansion part only) will be analyzed on the patients with unconfirmed CR or PR (dose escalation part) and confirmed CR or PR (expansion part) in the Full Analysis Set (Section 4). The number and percent of event (PD or death) and censord will be presented. The probability of being event-free at 3, 6, 9 and 12 months will be presented with its 95% CI. The estimated survival curves will be displayed graphically using Kaplan-Meier method.

Time to response and DoR based on investigator assessment and BICR assessment (expansion part only) will be presented in the form of patient data listings that include, but are not limited to, first dose date, date of first response, time to response, date of event or censoring, time to event or censoring, event type/censor and reason for censoring.

6.2.2.4. Progression Free Survival (PFS)

PFS based on investigator assessment and BICR assessment (expansion part only) will be analyzed on the Full Analysis Set (Section 4). The number and percent of event (PD or death) and censord will be presented. The probability of being event-free at 6, 12 and 18 months will be presented with its 95% CI. The estimated survival curves will be displayed graphically using Kaplan-Meier method.

PFS based on investigator assessment and BICR assessment (expansion part only) will be presented in the form of patient data listings that include, but are not limited to, first dose date, date of event or censoring, time to event or censoring, event type/censor and reason for censoring.

6.2.2.5. Overall Survival (OS)

OS will be analyzed on the Full Analysis Set (Section 4) in expansion part. The number and percent of event (death) and censord will be presented. The probability of being event-free at 12 months will be presented with its 90% CI. The estimated survival curves will be displayed graphically using Kaplan-Meier method.

OS will be presented in the form of patient data listings that include, but are not limited to, start date, date of event or censoring, time to event or censoring, event type/censor and reason for censoring.

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6.4. Subset Analyses

None

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Following data will be summarized and listed on the Full Analysis Set (Section 4).

- Demographic characteristics
  - Age (years)
  - Age in adult age categories; <18, 18-44, 45-64, ≥65 years
  - Gender; Male, Female
  - Race
  - Ethnicity
- Physical measurements
  - Weight (cm)
  - Height (kg)
  - BMI (kg/m^2)
- ECOG performace status
- General medical histories (coded by MedDRA preferred term; conditions are either Before or Ongoing)
- Disease characteristics
  - Primary diagnosis (coded by MedDRA preferred term)
  - Base of primary diagnoses
  - Histopathological grade; 1, 2, 3, 4, not reported (dose escalation part only)
  - Disease recurrence type (dose escalation part only)
  - Number of prior systemic medications; 0, 1, 2, 3, ≥4 regimens
  - Number of prior adjuvant and neo-adjuvant medications; 0, 1, 2, 3, ≥4 regimens

- Measurable disease by investigator assessment; yes, no, no disease
- Number of involved target tumor sites by investigator assessment; 1, 2, 3, ≥4 sites
- Number of involved non-target tumor sites by investigator assessment; 1, 2, 3, ≥4 sites
- Time since initial diagnosis (months)
- HER2 status; positive, negative (expansion part only)
- BRCA status; positive (BRCA1, BRCA2), negative (expansion part only)

- Prior therapies
  - Prior cancer therapy for primary diagnosis (coded by WHODrug preferred term)
  - Prior radiation therapy (coded by MedDRA preferred term)
  - Prior surgery (coded by MedDRA preferred term)

6.5.2. Study Conduct and Participant Disposition

Subject evaluation groups as shown below will be summarized and listed on the Enrolled population (Section 4).

- Not screen failure but not assigned
- Assigned to treatment
- Treated
- Not treated
- Full Analysis Set
- Per Protocol Analysis Set (dose escalation part only)
- Safety Analysis Set
- Pharmacokinetic Parameter Analysis Set (dose escalation part only)
- Pharmacokinetic Concentration Analysis Set

Inclusion and exclusion criteria and patients dispositions will be summarized and listed on the Enrolled population (Section 4).

6.5.3. Study Treatment Exposure

Study treatment exposure will be analyzed and listed on the Safety Analysis Set (Section 4).

- Duration of treatment (days): sum of the actual dosing day
- Total number of cycles started in each cohort
- Number of cycles started by patients
- Patients with maximum cycle started; 1, 2, 3, 4, ≥5 cycles
- Patients with at least one dose interruption
    - Maximum dose interruption in patients with at least one dose interruption; <1, 1 − <2, 2 − <3, ≥3 weeks
- Cumulative dose (mg): sum of the actual doses received in overall cycles
- Actual dose intensity (mg/day): the actual total dose divided by the actual number of days
- Relative dose intensity (%): the actual dose intensity divided by the intended dose
- Dose reductions due to any cause: no dose reduction; 1, 2, 3 dose level. Dose reduction is defined as non-zero dose less than the planned dose. The loweset dose level in overall treatment period will be summarized. One dose level is defined as 0.25 mg/day.

6.5.4. Concomitant Medications and Nondrug Treatments

Following data will be summarized and listed on the Safety Analysis Set (Section 4).

- Concomitant medications (coded by WHODrug preferred term)
- Concomitant nondrug treatments / procedures (coded by MedDRA preferred term)
- Follow-up cancer therapies (coded by WHODrug preferred term)
- Follow-up radiation therapies (coded by MedDRA preferred term)
- Follow-up surgeries (coded by MedDRA preferred term)

6.6. Safety Summaries and Analyses

All safety endpoints will be analyzed on the Safety Analysis Set (Section 4).

6.6.1. Adverse Events

The focus of AE summaries will be on Treatment Emergent Adverse Events (TEAEs) as defined in Section 3.5.1.

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest, by treatment group, primary System Organ Class (SOC) and Preferred Term (PT).

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst grade will be included in the summaries of relationship and grade.

In case a patient has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created by relationship (all causalities and treatment related):

- The overall summary of TEAEs table will include the number and percentage of patients with each of the following:
    - Any AEs
    - Serious AEs
    - Maximum grade 3 or 4 AEs
    - Maximum grade 5 AEs
    - AEs leading to discontinuation of study
    - AEs leading to discontinuation of study drug and continue study
    - AEs leading to interruption (temporary discontinuation) of study drug
    - AEs leading to dose reduction of study drug
- TEAEs by SOC and PT, and maximum grade
- TEAEs by decreasing frequency of PT with selected cluster terms

The following individual listings will be created:

- Deaths
- Serious AEs
- All AEs
- AEs leading to discontinuation of study

- AEs leading to discontinuation of study drug and continue study
- AEs leading to interruption (temporary discontinuation) of study drug
- AEs leading to dose reduction of study drug
- Medication errors

6.6.2. Laboratory Data

6.6.2.1. Parameters with NCI CTCAE Grades Available

The laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for NCI CTCAE grading (i.e. those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The summary of laboratory parameters by NCI CTCAE grade table will include number and percentage of patients with Grade 0, 1, 2, 3, 4 and Total, laboratory abnormalities during the on-treatment period.
- The shift table will summarize baseline NCI CTCAE grade versus the worst on-treatment NCI CTCAE grade. The highest NCI CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

Individual patients laboratory data listing will also be created with NCI CTCAE grading.

The above analyses apply to hematology and chemistry evaluations which can be graded per NCI CTCAE:

- Hematology:

  Hemoglobin, Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia), Triglycerides (hypertriglyceridemia).

6.6.2.2. Laboratory Assessment by Visit

Logitudinal absolute values and change from baseline values will be summarized and plotted in line graph with mean and 95% CI by visit in the following laboratory tests:

- Hematology: Hemoglobin, Leukocytes, Neutrophils and Platelets
- Chemistry: ALT, AST and Creatinine

6.6.2.3. Assessment of Possible Drug-Induced Liver Injury (DILI)

ALT, AST and total bilirubin (TBILI) during the on-treatment period are used to assess possible DILI. Multiples of upper limit of normal will be derived for each record. Maximum multiples of ALT or AST versus TBILI will be plotted in scatter plot as known the evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot.

6.6.2.4. Clinically Significant Abnormalities

The most abnormal values that met clinically significant abnormality criteria for each test will be listed by subject.

6.6.3. Vital Signs

For each vital sign assessment, actual and change from baseline values will be summarized by visit. The number and percentage of patients with vital sign values in specific categories (e.g., parameter measurements above or below a certain critical value) will be summarized (Table 8).

Table 8. Vital Signs Abnormal Categories (Position: Sitting)

Parameter (Unit)	Criteria
Systolic Blood Pressur (mmHg)	Value <90
	Change ≥30 increase
	Change ≥30 decrease
Diastolic Blood Pressure (mmHg)	Value <50
	Change ≥20 increase
	Change ≥20 decrease
Pulse Rate (beats/minite)	Value <40
	Value >120

All vital sign values described above will be listed.

6.6.4. Electrocardiograms

ECG measurements collected at nominal time-points will be used for the statistical analysis by visit. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding measurements. Interval measurements (e.g., triplicate measurements) from repeated ECGs will be included in the outlier analysis (categorical analysis) and shift table analysis of notable QTc parameters as individual values obtained at unscheduled time points.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be used to summarize the absolute values, changes from baseline and maximum change from baseline values by visit. Categorical analysis will be conducted for the individual values and maximum increase from baselin values, respectively (Table 9).

Table 9. Electrocardiograms Abnormal Categories (Unit: msec)

Parameter	Criteria	Parameter	Criteria
PR interval	Value ≥300	QT interval	Value ≥500
	%Change ≥25/50% [a]	QTc/QTcB/QTcF	450≤ Value <480
QRS interval	Value ≥200 (<18 Years)	interval	480≤ Value <500
	Value ≥140 (18-44 Years)		Value ≥500
	Value ≥140 (45-64 Years)		30≤ Change <60
	Value ≥140 (≥65 Years)		Change ≥60
	%Change ≥25/50% (<18 Years) [b]		
	%Change ≥50% (18-44 Years)		
	%Change ≥50% (45-64 Years)		
	%Change ≥50% (≥65 Years)		

a. Patients with Baseline value >200 or Baseline value ≤200, respectively
b. Patients with Baseline value ≥100 or Baseline value <100, respectively

Shift tables will be provided for baseline versus worst on-treatment QTc resutls (i.e., QTc, QTcF and QTcB) using maximum NCI CTCAE grade.

All ECG interval values (observed and derived) and qualitative ECG abnormalities will be listed.

6.6.5. Physical Examination

The findings in physical examination at screening visit will be listed by body system. Also post-baseline physical examination date will be listed.

6.6.6. ECOG Performance Status

The ECOG performance status shift from baseline to highest score during the on-treatment period will be summarized. ECOG performance status with shift from ECOG=0 or 1 to ECOG 2 or higher will also be presented in a data listing.

7. INTERIM ANALYSES

7.1. Introduction

There are no planned interim analyses. As this is an open-label to the investigators, patients and the Pfizer study team and uncontrolled study, interim analyses may be performed for study monitoring for internal decision making, application for approval or due to regulatory requests. There will be no need for unblinding and there are no issues of protecting the type 1 error rate.

7.2. Interim Analyses and Summaries

Not applicable

8. REFERENCES

1. Eisenhauer E, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guideline version 1.1. Eur J Can 2009; 45:228-47.

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9. APPENDICES

Appendix 1. Data Derivation Details

Appendix 1.1. Definition and Use of Visit Windows in Reporting

Visit windows will be used for any variables (e.g. laboratory tests, vital signs, ECGs) except PK measurements that display by visit (dose escalation part only). In general, Baseline visit will be displayed. Screening and Lead-in visits will be displayed, if appropriate.

Visit Label	Target Day	Definition [Day window]
Dose Escalation part		
Screening	Study Day -1	≤28 days prior to Lead-in [Study Day -28 to -1]
Lead-in	Study Day 1	Dosing day in Lead-in [Study Day 1]
Baseline	Study Day 1	Dosing start day in Study (i.e. Lead-in) [Study Day -28 to 1]
Cycle 1 Day 1	Cycle Day 1	Dosing start day in Cycle 1 [Cycle Day -1 to 1]
Cycle 1 Day 8	Cycle Day 8	[Cycle Day 7 to 9]
Cycle 1 Day 15	Cycle Day 15	[Cycle Day 14 to 16]
Cycle 1 Day 22	Cycle Day 22	[Cycle Day 21 to 23]
Cycle 2 Day 1	Cycle Day 1	Dosing start day in Cycle 2 [Cycle Day 1 to 3]
Cycle ≥3 Day 1	Cycle Day 1	Dosing start day in Cycle ≥3 [Cycle Day -2 to 3]
EoT	Not Applicable	End of Treatment
Expansion part		
Screening	Study Day -1	≤28 days prior to Lead-in [Study Day -28 to -1]
Baseline	Study Day 1	Dosing start day in Study [Study Day -28 to 1]
Cycle 1 Day 1	Cycle Day 1	Dosing start day in Cycle 1 [Cycle Day -3 to 1]
Cycle 1 Day 15	Cycle Day 15	[Cycle Day 12 to 18]
Cycle 2 Day 1	Cycle Day 1	Dosing start day in Cycle 2 [Cycle Day -3 to 1]
Cycle 2 Day 15	Cycle Day 15	[Cycle Day 12 to 18]
Cycle ≥3 Day 1	Cycle Day 1	Dosing start day in Cycle ≥3 [Cycle Day -3 to 1]

Visit Label	Target Day	Definition [Day window]
EoT	Not Applicable	End of Treatment

NOTE: If two or more visits fall into the same window, keep the one closest to the Target Day. If two visits are equal distant from the Target Day in absolute value, the later visit should be used.

Visit windows will be used for PK measurements in dose escalation part.

Period	Visit Label	Time Post Dose	Definition [Hour window]
Single Dose	Lead-in Day -7	0 Hour	Predose [No allowance]
	Lead-in Day -7	0.5 Hour	[within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample)]
	Lead-in Day -7	0.75 Hour	
	Lead-in Day -7	1 Hour	
	Lead-in Day -7	2 Hours	
	Lead-in Day -7	3 Hours	
	Lead-in Day -7	4 Hours	
	Lead-in Day -7	6 Hours	
	Lead-in Day -7	8 Hours	
	Lead-in Day -7	10 Hours	
	Lead-in Day -6	24 Hours	
	Lead-in Day -5	48 Hours	
	Lead-in Day -4	72 Hours	
	Lead-in Day -3	96 Hours	
	Cycle 1 Day 1	168 Hours	
	Cycle 1 Day 15	0 Hour	Predose [No allowance]
Multiple Dose	Cycle 1 Day 22	0 Hour	Predose [No allowance]
	Cycle 1 Day 22	0.5 Hour	[within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample)]
	Cycle 1 Day 22	0.75 Hour	
	Cycle 1 Day 22	1 Hour	
	Cycle 1 Day 22	2 Hours	
	Cycle 1 Day 22	3 Hours	
	Cycle 1 Day 22	4 Hours	
	Cycle 1 Day 22	6 Hours	
	Cycle 1 Day 22	8 Hours	
	Cycle 1 Day 22	10 Hours	
	Cycle 1 Day 23	24 Hours	
	Cycle 3 Day 1	0 Hour	Predose [No allowance]
	Cycle 4 Day 1	0 Hour	Predose [No allowance]

Appendix 1.2. Date of Last Contact

The date of last contact will be derived for patients not known to have died at the analysis data cutoff date using the latest complete date (non-imputed) among the following:

- All patient assessment dates (e.g., blood draws [laboratory, PK], vital signs, performance status, electrocardiogram, tumor assessments)
- Start and end dates of follow-up anti-cancer therapies including radiation and surgery
- Adverse event start and end dates
- Study drug start and end dates
- First dose date
- Date of discontinuation on disposition CRF pages (do not use if reason for discontinuation is lost to follow-up or death).

NOTE:

- Only dates associated with patient visits or actual examinations of the patient will be used. Dates associated with a technical operation unrelated to patient status (e.g., the date a blood sample was processed) will not be used.
- Assessment dates after the cutoff date will not be applied to derive the last contact date.