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

Investigational Product Number:	PF-06944076 (MDV3800/BMN673)
Investigational Product Name:	talazoparib
United States (US) Investigational New Drug (IND) Number:	Not Applicable
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	C3441030
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 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 design of the expansion part. • Schedule of Activities • Introduction • Study Objectives and Endpoints • Study Design • Patient Eligibility Criteria • Dose Reductions • Study Procedures • Pharmacokinetics Assessments • Tumor Response Assessments • Data Analysis/Statistical Methods. • New sections were added: Assessment of germline BRCA mutations for eligibility, CCI [redacted] In addition, administrative changes were made throughout the protocol associated with the expansion part including; • Background and Rationale have been updated to provide updated clinical data from the completed and ongoing clinical studies and with the current information about breast cancer. • Determination of Best Overall Response was added to Appendix 3. RECIST version 1.1

		Guidelines The following sections were updated according to the updated IB • Background and Rationale (safety and PK) • Lifestyle Requirements • Concomitant Treatment(s) Minor editorial changes were made for consistencies throughout the document.
Amendment 1	12 Sep 2017	Based on the requirement of Pharmaceuticals and Medical Devises Agency (PMDA), the following changes were incorporated. • Section 3.1 Study Overview For clarification, added the statement that RP2D may not be determined in some cases • Section 3.1.2. Criteria for Dose Escalation Updated the statement to clarify the process of dose escalation and RP2D determination. All of the safety data is potentially used for determination of dose escalation • Section 3.2. DLT Definition Grade ≥3 anemia requiring blood transfusion would be a DLT • 7.1.3. Laboratory Safety Assessment Added Red blood cell and Hematocrit in the hematology panel In overall, minor typographical error were corrected including reference update.
Original protocol	23 May 2017	Not applicable (N/A)

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

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

PROTOCOL SUMMARY

Background and Rationale

Cancer represents a disease area with a high-unmet medical need with more than 14.1 million people diagnosed annually worldwide, and an associated mortality that exceeds 8.2 million individuals[1]. The discovery and development of new anti-cancer therapies effective either in single-agent or combination treatment settings is still desperately needed.

Talazoparib (PF-06944076 also known as MDV3800 or BMN 673) is a potent, orally bioavailable, small molecule poly (adenosine diphosphate [ADP]-ribose) polymerase (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 deoxyribonucleic acid (DNA) repair, an effect referred to as synthetic lethality. In breast cancer MX-1 cells that are breast cancer susceptibility gene I (BRCA1) -deficient, talazoparib inhibits cell growth in vitro and inhibits tumor growth and/or induces tumor regression in mouse xenografts. Anti-tumor activity was also demonstrated in small cell lung cancer (SCLC) cell lines and xenograft models; single-agent talazoparib reduced tumor growth to a similar extent as the cytotoxic chemotherapy drug cisplatin in 2 independent SCLC xenograft models.

The main nonclinical toxicology findings with talazoparib were early hematologic changes and subsequent bone marrow and lymphoid organ depletion; focal atrophy and degeneration of the testes, epididymis, and seminiferous tubules; and dose-dependent apoptosis/necrosis in the gastrointestinal (GI) tract and liver after repeat-dose administration of talazoparib. These findings are consistent with the exaggerated pharmacology of talazoparib and its tissue exposure pattern. The hematologic findings were generally reversible and the early hematologic changes represent sensitive and early markers of target organ toxicity. Talazoparib caused fetal malformations, structural variations, and death in an embryo-fetal development study in rats.

As of 31 January 2018, approximately 659 patients and 18 healthy volunteers have received talazoparib at doses up to 2 mg/day in company-sponsored clinical studies in hematologic malignancies and solid tumors. The majority of available efficacy and safety data was obtained from studies in solid tumors. A phase 1 study in patients with advanced or recurrent solid tumors defined the maximum tolerated dose (MTD) of talazoparib as 1 mg/day. Data from the C3441030 study demonstrated objective responses and/or clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer; SCLC; and Ewing sarcoma.

Treatment-emergent adverse drug reactions (ADRs) of all causality reported in ≥20% of patients administered single-agent talazoparib 1 mg/day are related to myelosuppression (anemia, thrombocytopenia, neutropenia), GI toxicity (nausea, diarrhea, vomiting, abdominal pain, and decreased appetite), fatigue, headache, and alopecia. Grade 3 or 4 ADRs of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) in ≥5% of patients were associated with myelosuppression. The ADRs associated with talazoparib are generally detected through routine laboratory and clinical monitoring and may be managed using symptomatic therapies, supportive care, or dose reductions or interruptions.

The pharmacokinetics (PK) of talazoparib as a single agent was evaluated in patients with hematologic malignancies and solid tumors at doses of 0.025 to 2 mg/day administered orally, as a single dose or as multiple doses. The PK was similar in patients of each cancer type and no differences were apparent between males and females. Oral absorption of talazoparib was rapid and independent of dose after administration of single or multiple doses. Elimination appeared to follow biphasic kinetics; the mean terminal half life ($t_{½}$) was approximately 4 days. Talazoparib accumulated after 1 mg quaque die (QD) dosing with a median accumulation ratio (R_{ac}) ranging from 2.33 to 5.15, consistent with its $t_{½}$. Steady state was reached around 3 weeks after the start of talazoparib dosing. Talazoparib undergoes minimal hepatic metabolism in humans. Renal excretion was a major elimination pathway for unchanged parent talazoparib. A food-effect study showed that food had no clinically meaningful effect on the extent of absorption; talazoparib is being administered without regard to food in ongoing safety and efficacy studies.

At therapeutic exposures, talazoparib did not markedly induce or inhibit cytochrome P450 (CYP450) enzymes or transporters and is therefore unlikely to demonstrate clinically significant CYP450 inhibition- or induction-based drug-drug interactions (DDIs) or drug transporter inhibition-based DDIs when coadministered with corresponding substrates. However, talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and plasma talazoparib concentrations may increase when coadministered with P-gp or BCRP inhibitors, respectively.

A phase 2 (ABRAZO, 673-201, C3441008) and a phase 3 (EMBRACA, 673-301, C3441009) study evaluated single-agent talazoparib in patients with locally advanced or metastatic breast cancer with deleterious germline BRCA mutations (gBRCAm). EMBRACA met primary endpoint and is following-up for OS. However Japanese patients were not included in these studies and there was no clinical experience with talazoparib in Japanese patients, at the time of study initiation. Therefore, the current C3441030 study was initially designed to evaluate the safety, tolerability, preliminary efficacy, and PK profile of talazoparib as a single agent in Japanese patients with advanced solid tumors (the dose escalation part).

As of 24 January 2019, a total of 9 patients were enrolled in the dose escalation part of the C3441030 study. Dose limiting toxicities (DLT) were not reported in any patients receiving 0.75 mg/day (n=3) or 1.0 mg/day (n=6). Therefore, the recommended Phase 2 dose (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.

EMBRACA is a pivotal, randomized, open label, 2 arm, Phase 3 study that evaluated talazoparib versus protocol specified physician's choice treatment (PCT) in patients with gBRCAm HER2-negative locally advanced or metastatic breast cancer. PCT included single agent capecitabine, eribulin, gemcitabine, or vinorelbine and was determined by the treating physician for each patient before randomization. The primary objective of the study was to

compare progression-free survival (PFS) by blinded independent central review (BICR) assessment between the talazoparib and PCT arms. As of data cutoff date of 15 September 2017, the study met its primary objective demonstrating that talazoparib was superior to chemotherapy in prolonging PFS by BICR assessment, with the median PFS of 8.6 months [95% confidence interval (CI): 7.2, 9.3] in talazoparib arm compared with 5.6 months (95% CI: 4.2, 6.7) in PCT arm. There was a 46% reduction in relative risk of disease progression or death, with an observed hazard ratio (HR) of 0.54 (95% CI: 0.41, 0.71; p<0.0001 [2-sided by stratified log-rank test]). The primary analysis of objective response rate (ORR) was conducted in the intent-to-treat (ITT) with measurable disease population, based on investigator assessment. ORR was 62.6% (95% CI: 55.8, 69.0) in the talazoparib arm vs 27.2% (95% CI: 19.3, 36.3) in PCT arm. The odds ratio was 4.99 (95% CI: 2.9, 8.8) with a p-value from the 2-sided stratified Cochran-Mantel-Haenszel test of <0.0001 in favor of the talazoparib arm. Although confirmation was not required for this randomized trial, the confirmed ORR by investigator's assessment was 50.2% (95% CI: 43.4, 57.0) in talazoparib arm and 18.4% (95% CI: 11.8, 26.8) in PCT arm. An interim analysis of overall survival (OS) was conducted (163 deaths had occurred). Median OS was 22.3 months (95% CI: 18.1, 26.2) in the talazoparib arm and 19.5 months (95% CI: 16.3, 22.4) in the PCT arm with the estimated HR of 0.76 (95% CI: 0.55, 1.06; p=0.1053 [2-sided by stratified log-rank test]).

Following on the encouraging results of EMBRACA and the determination of RP2D in Japanese patients, the C3441030 study will be 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. It will also explore biomarkers in blood and tumor samples that includes attempts to characterize sensitivity and resistance to talazoparib.

Objectives and Endpoints

Dose Escalation Part (Solid Tumor)

Primary Objective

- 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/schedule in Japanese patients

Secondary Objectives

- To evaluate the overall safety profile
- To characterize the single and steady state PK of single-agent talazoparib
- To assess preliminary evidence of anti-tumor activity of single-agent talazoparib

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Endpoints

Primary Endpoint

- First-cycle DLTs

Secondary Endpoints

- AEs as characterized by type, frequency, severity (as graded by the NCI CTCAE, Version 4.03), timing, seriousness, and relationship to talazoparib
- Laboratory abnormality as characterized by type, frequency and severity (graded by the NCI CTCAE, Version 4.03), and timing
- Vital signs
- Pharmacokinetic parameters of talazoparib
- Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, V_z/F, $t_{½}$, and AUC_{inf} as data permit
- Multiple Dose (MD) (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, CL/F, R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$), $C_{ss,min}$ and R_{ss} ($AUC_{ss,\tau}$ /$AUC_{sd,inf}$) as data permit
- Objective Response (OR), as assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Time to event endpoints: Duration of Response (DoR) and PFS if applicable

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Expansion Part (gBRCAm breast cancer)

Primary Objective

- To evaluate the anti-tumor activity of single agent talazoparib in Japanese patients with gBRCAm HER2-negative locally advanced or metastatic breast cancer

Secondary Objectives

- To further evaluate anti-tumor activity
- To evaluate the overall safety profile of talazoparib
- To characterize the PK of single-agent talazoparib

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Endpoint

Primary Endpoint

- Confirmed OR as assessed using RECIST version 1.1 by Investigator Assessment

Secondary Endpoints

- 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
- Trough concentrations of talazoparib
- OR as assessed using RECIST version 1.1 by 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

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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/day and 1.0 mg/day.

Single-dose safety and single-dose PK assessments of talazoparib in 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 which is designed to assess the efficacy, safety and PK 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 study. The expansion part will include 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.

Study Treatments

Talazoparib will be administered on a continuous basis once daily taken at the same time with or without food. A cycle is defined as the time from Day 1 dose of one cycle to the next Day 1 dose of the next Cycle. If there are no treatment delays, a cycle will be 28 days.

Talazoparib will be provided as capsules for oral administration. The 0.25 mg capsules will be supplied in separate bottles (or blister cards, as appropriate) and labeled according to local regulatory requirements. For the expansion part, 1.0 mg capsule will also be supplied as a starting dose; 0.25 mg capsule should only be used for patients who require dose reduction.

Statistical Methods

DLT is the primary endpoint of the dose escalation part of the study. The occurrence of DLTs observed in the first cycle of each cohort is used to evaluate the RP2D as described in the Study Design section. AEs constituting DLTs will be listed per dose level.

For the expansion part, the confirmed ORR assessed using RECIST version 1.1 by Investigator Assessment and the exact two-sided 90% CI will be calculated.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Assessments section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the patient.

[Dose Escalation part]

		Lead in	CYCLE 1				CYCLE ≥2		
Visit Identifier (Visit or Assessment window [days] unless otherwise noted) [a]	**Screening** [b] **(≤28 days prior to Lead-in)**	**Day -7 (-1)**	**Day 1(-1)**	**Day 8 (±1)**	**Day 15 (±1)**	**Day 22 (±1)**	**Day 1(±2)** [c]	**End of Treatment** [d]	**Follow- up** [e]
Informed consent [f]	X						(X)		
Tumor history	X								
Medical history	X								
Physical examination	X	X	X				X	X	
Baseline signs and symptoms [g]	X								
Height	X								
Weight	X	X	X				X	X	
Vital signs [h]	X	X	X		X			X	
Performance status [i]	X		X				X	X	
Laboratory									
Hematology [j]	X	X	X	X	X	X	X	X	
Blood Chemistry [k]	X	X	X	X	X	X	X	X	
Urinalysis [l]	X							X	
Pregnancy test [m]	X	X					X	X	X
Virus test (HBV/HCV/HIV) [n]	X								
Contraception check [o]	X	X	X				X	X	
(12 lead) ECG [p]	X	X	X			X	X	X	

		Lead in	CYCLE 1				CYCLE ≥2		
Visit Identifier (Visit or Assessment window [days] unless otherwise noted) [a]	**Screening [b] (≤28 days prior to Lead-in)**	**Day -7 (-1)**	**Day 1(-1)**	**Day 8 (±1)**	**Day 15 (±1)**	**Day 22 (±1)**	**Day 1(±2) [c]**	**End of Treatment [d]**	**Follow- up [e]**
Registration and Treatment									
Registration [q]	X								
Study treatment [r]		X	X	→	→	→	→		
Tumor assessments	X						X	X	
CT or MRI scan or equivalent [s]	X						X	X	
Other clinical assessments									
Serious and non-serious adverse event monitoring [t]	X	→	→	→	→	→	→	→	→
Concomitant treatment(s) [u]	X	→	→	→	→	→	→	→	X
Other samplings									
Pharmacokinetics [v]		X	X		X	X	X		
CCI [redacted]		C							

Abbreviations: → = ongoing/continuous event; CT = computed tomography; ECG = electrocardiogram; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging.

a. Day relative to start of study treatment (Day 1).
b. Screening: To be obtained within 28 days prior to Cycle 1 Day -7 (C1D-7).
c. For Cycle 2 Day 1 (C2D1), "-2 days" window is not applicable.
d. End of Treatment Visit: Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments)
e. Follow-up: At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed until resolution or determination, in the clinical judgment of the investigator and consultation with the sponsor, that no further improvement is expected. Pregnancy test will be performed for women of childbearing potential only.
f. Informed Consent: Must be obtained prior to undergoing any study-specific procedures. Procedures performed as standard of care prior to signed and dated informed consent document (ICD), and within the 28 day screening window may be used for study eligibility. Patients must be also asked to sign an additional consent document before starting treatment on C2D1 for confirmation of their willingness to continue participation in the study beyond Cycle 1.
g. Baseline Signs & Symptoms: Patients will be asked about any signs and symptoms experienced within the 14 days prior to PK lead-in dose. Clinically significant baseline signs and symptoms will be recorded on the Adverse Event case report form (CRF) page.
h. Vital Signs: Blood pressure (BP) and pulse rate to be recorded in sitting position.
i. Performance Status: Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 4
j. Hematology: No need to repeat on C1D-7 if baseline assessment performed within 7 days prior to that date. Additional hematology may be performed as clinically indicated. Frequency should be increased as clinically indicated to monitor neutropenia, thrombocytopenia, and anemia. See Assessments section for Laboratory Tests list.
k. Blood Chemistry: No need to repeat on C1D-7 if baseline assessment performed within 7 days prior to that date. Additional chemistries may be performed as clinically indicated. See Assessments section for Laboratory Tests list.
l. Urinalysis: Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D-7 if baseline assessment performed within 7 days prior to that date. Additional urinalysis may be performed as clinically indicated. See Assessments section for Laboratory Tests list.
m. Pregnancy Test (for women of childbearing potential only): described in the Pregnancy Testing section.
n. Virus (HBV/HCV/HIV) test: Perform within 28 days prior to the first study treatment.
o. The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly. Also, for studies enrolling adult patients, it is the opportunity to assess changing potential to father/bear children and allows for altering contraception if new disease contraindicates a selected method of contraception or if nonchildbearing status is achieved.
p. 12-Lead ECG: A single 12-lead ECG will be performed. No need to repeat on C1D-7 if baseline assessment performed within 7 days prior to that date. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the QTcF is prolonged (>500 msec), 3 consecutive 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.
q. Registration: patient number and dose level allocation assigned by Pfizer Inc.

r. Study Treatment: described in the Study Treatments section. A single dose of tralazoparib is administered on C1D-7, then continuous dose will begin from C1D1.

s. Tumor Assessments: Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans. Brain scans and bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. CT or MRI scans to be done on C2D1 and Day 1 of every other cycle (e.g. C4, C6, C8, C10 and C12) ±7 days window. No need to repeat if the start of new cycle delays (e.g. due to treatment related toxicity). After completion of Cycle 12, tumor assessment will be done per local standard practice. Tumor assessment should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation. Given the exploratory nature of the dose escalation part, confirmation of response (complete response [CR]/partial response [PR]) is not required. As clinically indicated, CT/MRI will be repeated by investigator's discretion.

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

u. Concomitant Treatments: all concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF.

v. PK Sampling: Blood will be collected for PK sampling of talazoparib. In lead in phase, after a single dose of tarazoparib, samples at predose and 0.50, 0.75, 1, 2, 3, 4, 6, 8, 10 hour (h) on C1Day -7. After that, 24, 48, 72 and 96 h post dose samples will be collected on through C1D-6 to C1D-3. Pre-dose sample will be collected on C1D1 dosing as 168 h post dose sample. Pre-dose samples will be collected on C1Day 15. Serial PK samples after multiple dose will be collected on C1D22 at predose, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 10 h. Pre-dose samples will be collected on C1D23 and Day 1 of Cycles 3 and 4. Details are in Pharmacokinetic Sampling Schema.

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Pharmacokinetic Sampling Schema

Visit Identifier	**Lead in**														**CYCLE 1**														**CYCLE 3**	**CYCLE 4**
Study Day	**Day -7**										**-6**	**-5**	**-4**	**-3**	**Day 1**	**15**	**22**										**23**	**Day 1**	**Day 1**
Hours Before/After Dose	**0 [a]**	**0.5**	**0.75**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**24**	**48**	**72**	**96**	**168 [a]**	**0 [a]**	**0 [a]**	**0.5**	**0.75**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**24 [a]**	**0 [a]**	**0 [a]**
Study treatment administration	X														X	X	X										X	X	X
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviation: PK = pharmacokinetic.

a. Predose sample collection. Study treatment administration should be after the PK blood sampling.

[Expansion part]

	Screening [a]	CYCLEs 1 and 2 [b]		CYCLEs ≥ 3 [b]	End of Treatment [c]	Long-Term Follow-Up [d]
Procedure/Assessment (visit window) [e]	**(-28 days prior to first dose of study treatment)**	**Day 1 (-3 days)**	**Day15 (±3 days)**	**Day1 (-3 days)**	**28 days postdose (+7 days)**	**See footnote [d] for schedule**
Informed consent [f]	X					
Medical history [g]	X					
Vital signs [h]	X	X	X	X	X	
Physical examination [i]	X	X		X	X	
ECOG Performance Status	X	X		X	X	
Tumor assessment [j]	X	X (See footnote [j])			X	
Bone scan [j]	X	[X] (See footnote [j])			[X]	
PK blood sampling [k]		X		X		
Clinical laboratory tests						
Hematology [l]	X	X	X	X	X	
Serum chemistry [l]	X	X		X	X	
Urinalysis [l]	X					
Calculated creatinine clearance [l]	X					
Virus test (HBV/HCV/HIV) [m]	X					
Pregnancy test [n]	X	X		X	X	
Serious and non-serious adverse event monitoring [o]	X	X	X	X	X	
Contraception check [p]	X	X		X	X	
(12 lead) ECG [q]	X				X	
Concomitant medications [r]	X	X	X	X	X	
Patient contact: survival, obtain cancer treatment						X
Talazoparib treatment [s]		Once-daily dosing				

	Screening [a]	CYCLEs 1 and 2 [b]		CYCLEs ≥ 3 [b]	End of Treatment [c]	Long-Term Follow-Up [d]
Procedure/Assessment (visit window) [e]	**(-28 days prior to first dose of study treatment)**	**Day 1 (-3 days)**	**Day15 (±3 days)**	**Day1 (-3 days)**	**28 days postdose (+7 days)**	**See footnote [d] for schedule**
Documentation of germline BRCA1 or BRCA2 mutation [t]	[X]					
Blood sample (germline BRCA assay) [u]	X					
[redacted]	[redacted]					
[redacted]		[redacted]			[redacted]	
[redacted]	[redacted]					
[redacted]	[redacted]				[redacted]	

[X] denotes an optional test. Abbreviations: AE = adverse event; BRCA = breast cancer susceptibility gene; CT = computed tomography; [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; NCI CTCAE = the National Cancer Institute Common Terminology Criteria for Adverse Events; PK = pharmacokinetics; SAE = serious adverse event.

a. Screening: The Screening visit must occur within 28 days before starting study treatment. Screening and baseline procedures may be performed on the same day as long as it is within 7 days before starting therapy.

b. The first day of treatment in each Cycle is defined as Day 1.

c. End of treatment visit: Obtain these assessments at the time of treatment discontinuation if not completed in the last week. Pregnancy test will be performed for women of childbearing potential only.
At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed until resolution or determination, in the clinical judgment of the investigator and consultation with the sponsor, that no further improvement is expected.

d. Long-term Follow-up: Patient contact for: survival, cause of death, and additional cancer treatment every 3 months (±7 days) after last dose for 1 year, every 6 months (±14 days) thereafter, or whenever requested by the Sponsor.

e. All assessments will be performed before dosing except as indicated. Additional tests/procedures and/or unscheduled visit can be performed as clinically indicated.

f. Informed Consent: Must be obtained prior to undergoing any study-specific procedures. Procedures performed as standard of care prior to signed and dated informed consent document (ICD), and within the 28-day screening window may be used for this study. Written informed consent for only the BRCA1/2 mutation testing blood test may be obtained at any time (including prior to the screening period).

g. Medical History: Includes full oncologic history, prior treatments, and demographics. Clinically significant baseline signs and symptoms will be recorded as medical history.

h. Vital Signs: Systolic and diastolic blood pressure, pulse rate to be recorded as defined in the Schedule of Activities and weight at Screening, Day 1 of each cycle and End of Treatment; height at Screening only.

i. Physical Examinations: Screening physical examination to be a complete exam; subsequent examinations to be focused on physical examinations at the discretion of the Investigator based on the patient's clinical condition.

j. Imaging includes chest, abdomen, and pelvis CT (recommended) or MRI scans. A brain MRI or CT is to be performed at Screening to evaluate patients for presence/absence of brain metastases. Newly diagnosed CNS metastases at Screening makes a patient ineligible until such time as it can be adequately treated, at which point the patient may be re-screened. If adequately treated metastatic disease to the brain is present at Screening, an MRI or CT will be performed during the study as clinically indicated. Post-baseline assessments should be performed using the same technique used at Screening. CT/MRI scans performed as standard of care before the main ICD was signed and within the 28-day screening period may be used as the Screening tumor assessments if the scans were completed per the specific study requirements.
Tumor assessment to be performed every 6 weeks (±7 days) from the date of initial study treatment (C1D1) for the initial 24 weeks and every 8 weeks (±7 days) thereafter, until objective disease progression or treatment discontinuation, regardless of any dose interruptions or dose delays. According to RECIST ver 1.1, complete response (CR) and partial response (PR) must be confirmed by a second image at least 4 weeks from the initial imaging showing response. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation. Tumor assessments can occur as clinically indicated anytime during the study, and at the time of clinical suspicion of disease progression. Post-baseline tumor assessments should be performed using the same technique used at Screening/baseline.
Bone scan will be performed at Screening (a bone scan obtained up to 12 weeks before starting study treatment may be substituted). If metastatic disease to the bone is present at Screening, a bone scan will be performed every 12 weeks (±7 days) for the initial 24 weeks and every 16 weeks (±7 days) thereafter,

and as clinically indicated. Post-baseline assessments should be performed using the same technique used at Screening.
All scans taken for this study have to be submitted for Blinded Independent Central Review (BICR). Once study endpoints are summarized and they are notified by Sponsor, tumor assessment including brain and bone scan can be done per local standard practice and the requirement of imaging submission is no longer applicable.

k. PK blood sampling: Trough PK samples will be collected on Day 1 of Cycles 2 through 4. In the event of a dose delay on the day of PK sampling, the pre-dose PK sample should be drawn on the day the patient resumes their next dose of talazoparib.

l. Hematology: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Frequency should be increased as clinically indicated to monitor neutropenia, thrombocytopenia, and anemia. See Assessments section for Laboratory Tests list.
Serum chemistry: No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests list.
Urinalysis (dipstick): Microscopic analyses if dipstick abnormal. See Assessments section for Laboratory Tests list.
Calculated creatinine clearance: to be performed at Screening. Use local laboratory results or calculate by Cockcroft-Gault formula.

m. Virus (HBV/HCV/HIV) test: Perform within 28 days prior to the first study treatment.

n. Pregnancy test (for women of child-bearing potential only): Local urine or serum (as per local regulations/practice) pregnancy test should be performed at Day 1 of each cycle, prior to administration of study medication; if a urine pregnancy test is positive, study drug must be interrupted and a serum pregnancy test must be performed. Additional pregnancy testing may be performed throughout the study as clinically indicated.

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

p. The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly. Also, for studies enrolling adult patients, it is the opportunity to assess changing potential to father/bear children and allows for altering contraception if new disease contraindicates a selected method of contraception or if nonchildbearing status is achieved.

q. 12-Lead ECG: 12-lead ECG to be performed at Screening and End of Treatment, if clinically indicated. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the QTcF is prolonged (>500 msec), 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 site for confirmation. Additional ECGs may be performed as clinically indicated.

r. Concomitant treatments: All concomitant medications or therapies, including herbal supplements, taken from 28 days before study treatment to 28 days after the last dose will be recorded on the CRF.

s. Talazoparib treatment: Talazoparib will be administered orally daily for 28 days in repeated 28-day cycles. On selected days of clinic visits, the drug will be taken at the clinic to allow pre-dose collection of safety data.

t. With Sponsor preapproval, results (documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation) generated previously using the BRACAnalysis CDx test, may be provided to meet this molecular enrollment criterion.

u. For patients who must undergo prospective BRCA germline testing, blood sample must be collected for testing as early as possible during the screening period. BRCA germline testing can be done outside of 28-day Screening period for patients who provide ICD for the BRCA1/2 mutation testing.

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

Talazoparib is a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor that is currently being investigated in patients with solid tumors including germline breast cancer susceptibility gene mutation (gBRCAm) locally advanced and metastatic breast cancer.

1.2. Background and Rationale

Cancer represents a disease area with a high-unmet medical need with more than 14.1 million people diagnosed annually worldwide, and an associated mortality that exceeds 8.2 million individuals[1]. Breast cancer is the second most common cause of cancer deaths in women, despite improvements in screening and treatment regimens. According to the World Health Organization, in 2012, 1.7 million women were diagnosed with breast cancer and over 522,000 women died due to the disease[2]. In Japan, it was estimated that approximately 13,000 women died due to breast cancer, which was approximately 9% of total death in cancer death in 2013[3]. The discovery and development of new anti-cancer therapies effective either in single-agent or combination treatment settings is still desperately needed.

1.2.1. Role of BRCA and PARP in DNA repair

Cancers are caused by multiple genetric and/or environmental factors. Consequent genome instability and deficiency of DNA repair mechanism (e.g. base excision repair, mismatch repair, homologous recombination etc) enable tumor development. BRCA1 and BRCA2 are tumor suppressor gene, and the product of BRCA genes play an important role of maintaining genomic stability in part by contributing to DNA repair of double-stranded breaks. Loss of BRCA function due to pathogenic mutations in BRCA may cause homologous recombination deficiency (HRD).

Breast cancer is a biologically diverse and genetically heterogeneous disease[4,5]. Germline mutations in BRCA1/2 result in a lifetime risk of breast cancer by age of 70, of up to 80%[6]. It was suspected that approximately 5% to 10% of breast cancer in women are associated with germline BRCA1 or BRCA2 mutations. Estrogen receptor negative, progesterone receptor (PgR) negative, HER2-negative tumors are known as triple negative breast cancer (TNBC). Characterization of BRCA1 mutated breast cancers are known to be TNBC (70%), solid-tubular carcinoma and high histopathological grade[7]. Hormone receptor-positive tumors were more frequent in BRCA2 mutation carriers[8].

PARPs comprise a family of at least 17 enzymes that transfer ADP-ribose groups to target proteins to regulate various cellular processes, including DNA repair; PARP1 and PARP2 play important roles in DNA repair[9,10]. Following DNA damage, PARP1 and PARP2 bind to single-strand DNA breaks, cleave nicotinamide adenine dinucleotide (NAD^+), and attach multiple ADP-ribose units to target proteins, including itself[11,12,13,14]. The outcome is a highly negatively charged protein, which leads to the unwinding of the DNA strands and recruitment of proteins to repair the damaged DNA through the base excision repair (BER) process. When PARP1 and PARP2 are inhibited, single-strand DNA breaks persist, resulting

in PARP trapping, stalled replication forks and conversion of single-strand breaks into double-strand breaks. These breaks must be repaired by homologous recombination or nonhomologous end joining or they may become lethal.

1.2.2. Mechanism and clinical use of PARP inhibitor to BRCA mutated cancer

PARP inhibitors exert cytotoxic effects by 2 mechanisms, (1) inhibition of PARP catalytic activity and (2) PARP trapping, whereby PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, preventing DNA repair, replication, and transcription[15]. Inhibition of PARP catalytic activity results in persistent single-strand breaks that require homologous recombination DNA repair for survival. When trapped, PARP-DNA complexes inhibit DNA repair, replication, and transcription, and are more cytotoxic than unrepaired single-strand breaks because they do not readily dissociate. Importantly, the ability to trap PARP-DNA complexes varies widely across the different PARP inhibitors, correlates with cell toxicity in tissue culture, and does not correlate with PARP catalytic inhibition.

DNA instability is an important characteristic of many tumor types, often times a consequence of defects in DNA repair[16]. Although a single DNA repair pathway defect may not be lethal to the cell, the combination of 2 pathway defects may be lethal. This outcome is an example of synthetic lethality[17]. PARP inhibitors induce synthetic lethality in tumor cells bearing mutations and/or deletions in genes involved in homologous recombination DNA repair pathways, including BRCA1, BRCA2, FANCA, PTEN, RAD51, MLH1, MSH2, ATM, MRE11, and PALB2[18,19,20,21,22,23,24,25]. In BRCA1- and BRCA2-deficient cells, treatment with a PARP inhibitor results in cell cycle arrest and apoptosis[26,27,28]. Proof-of-concept clinical studies in patients with ovarian, breast, and prostate cancers showed responses to PARP inhibitor therapy in those with BRCA1 and BRCA2 mutations[29,30,31,32], establishing the clinical relevance of PARP inhibitor-induced synthetic lethality in patients with tumors harboring BRCA mutations.

The prevalence of DNA repair deficiencies contributing to synthetic lethality varies with tumor type. In metastatic castration-resistant prostate cancer, analysis of somatic and germline mutation status demonstrated that 22.7% of cases had mutations in DNA repair genes associated with sensitivity to a PARP inhibitor including BRCA2, BRCA1, CDK12, FANCA, RAD51B, RAD51C, MLH1, and ATM[33]. In an independent phase 2 study, 16 of 49 evaluable patients (33%) with metastatic castration-resistant prostate cancer had mutations and/or deletions in genes involved in homologous recombination or other DNA repair pathways. Of the 16 patients (33%) who responded to treatment with olaparib, 14 (88%) had mutations in DNA repair genes[26]. These data suggest that PARP inhibition may be a useful strategy in a broad array of tumor types bearing diverse DNA repair pathway deficiencies that extend beyond BRCA1/2 mutations.

In gBRCAm metastatic breast cancer, positive outcomes have been reported in a global phase 3 study of olaparib (a PARP inhibitor) comparing to the standard single-agent chemotherapy, demonstrating statistically significant prolongation of progression-free survival (PFS) in the olaparib arm which supported the approval by the US Food and Drug Administration (FDA) and the Japan Ministry of Health, Labour and Welfare (MHLW) for use in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer.

1.2.3. Talazoparib and available non-clinical/clinical data

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. In breast cancer MX-1 cells that are BRCA1-deficient, talazoparib inhibits cell growth in vitro and inhibits tumor growth and/or induces tumor regression in mouse xenografts. Anti-tumor activity was also demonstrated in small cell lung cancer (SCLC) cell lines and xenograft models; single-agent talazoparib reduced tumor growth to a similar extent as the cytotoxic chemotherapy drug cisplatin in 2 independent SCLC xenograft models.

The main nonclinical toxicology findings with talazoparib were early hematologic changes and subsequent bone marrow and lymphoid organ depletion; focal atrophy and degeneration of the testes, epididymis, and seminiferous tubules; and dose-dependent apoptosis/necrosis in the GI tract and liver after repeat-dose administration of talazoparib. These findings are consistent with the exaggerated pharmacology of talazoparib and its tissue exposure pattern. The hematologic findings were generally reversible and the early hematologic changes represent sensitive and early markers of target organ toxicity. Talazoparib caused fetal malformations, structural variations, and death in an embryo-fetal development study in rats.

As of 31 January 2018, approximately 659 patients and 18 healthy volunteers have received talazoparib at doses up to 2 mg/day in company-sponsored clinical studies in hematologic malignancies and solid tumors. The majority of available efficacy and safety data was obtained from studies in solid tumors. A phase 1 study in patients with advanced or recurrent solid tumors defined the maximum tolerated dose (MTD) of talazoparib as 1 mg/day. Data from the C3441030 study demonstrated objective responses and/or clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer; SCLC; and Ewing sarcoma.

Treatment-emergent adverse drug reactions (ADRs) of all causality reported in ≥20% of patients administered single-agent talazoparib 1 mg/day are related to myelosuppression (anemia, thrombocytopenia, neutropenia), GI toxicity (nausea, diarrhea, vomiting, abdominal pain, and decreased appetite), fatigue, headache, and alopecia. Grade 3 or 4 ADRs of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) in ≥5% of patients were associated with myelosuppression. The ADRs associated with talazoparib are generally detected through routine laboratory and clinical monitoring and may be managed using symptomatic therapies, supportive care, or dose reductions or interruptions.

The pharmacokinetics (PK) of talazoparib as a single agent was evaluated in patients with hematologic malignancies and solid tumors at doses of 0.025 to 2 mg/day administered orally, as a single dose or as multiple doses. The PK was similar in patients of each cancer type and no differences were apparent between males and females. Oral absorption of talazoparib was rapid and independent of dose after administration of single or multiple doses. Elimination appeared to follow biphasic kinetics; the mean terminal half life ($t_{½}$) was approximately 4 days. Talazoparib accumulated after 1 mg quaque die (QD) dosing with a median accumulation ratio (R_{ac}) ranging from 2.33 to 5.15, consistent with its $t_{½}$. Steady state was reached around 3 weeks after the start of talazoparib dosing. Talazoparib undergoes

minimal hepatic metabolism in humans. Renal excretion was a major elimination pathway for unchanged parent talazoparib. A food-effect study showed that food had no clinically meaningful effect on the extent of absorption; talazoparib is being administered without regard to food in ongoing safety and efficacy studies.

At therapeutic exposures, talazoparib did not markedly induce or inhibit cytochrome P450 (CYP450) enzymes or transporters and is therefore unlikely to demonstrate clinically significant CYP450 inhibition- or induction-based drug-drug interactions (DDIs) or drug transporter inhibition-based DDIs when coadministered with corresponding substrates. However, talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and plasma talazoparib concentrations may increase when coadministered with P-gp or BCRP inhibitors, respectively.

A phase 2 (ABRAZO, 673-201, C3441008) and a phase 3 (EMBRACA, 673-301, C3441009) study evaluated single-agent talazoparib in patients with locally advanced or metastatic breast cancer with deleterious gBRCAm.

EMBRACA is a pivotal, randomized, open label, 2 arm, Phase 3 study that evaluated talazoparib versus protocol specified physician's choice therapy (PCT) in patients with gBRCAm HER2-negative locally advanced or metastatic breast cancer. PCT included single agent capecitabine, eribulin, gemcitabine, or vinorelbine and was determined by the treating physician for each patient before randomization. The primary objective of the study was to compare PFS by Blinded Independent Central Review (BICR) assessment between the talazoparib and PCT arms. As of data cutoff date of 15 September 2017, the study met its primary objective demonstrating that talazoparib was superior to chemotherapy in prolonging PFS by BICR assessment, with the median PFS of 8.6 months [95% confidence interval (CI): 7.2, 9.3] in talazoparib arm compared with 5.6 months (95% CI: 4.2, 6.7) in PCT arm. There was a 46% reduction in relative risk of disease progression or death, with an observed hazard ratio (HR) of 0.54 (95% CI: 0.41, 0.71; p<0.0001 [2-sided by stratified log-rank test]). The primary analysis of objective response rate (ORR) was conducted in the intent-to-treat (ITT) population with measurable disease population, based on Investigator assessment. ORR was 62.6% (95% CI: 55.8, 69.0) in the talazoparib arm vs 27.2% (95% CI: 19.3, 36.3) in PCT arm. The odds ratio was 4.99 (95% CI: 2.9, 8.8) with a p-value from the 2-sided stratified Cochran-Mantel-Haenszel test of <0.0001 in favor of the talazoparib arm. Although confirmation was not required for this randomized trial, the confirmed ORR by investigator's assessment was 50.2% (95% CI: 43.4, 57.0) in talazoparib arm and 18.4% (95% CI: 11.8, 26.8) in PCT arm. An interim analysis of overall survival (OS) was conducted (163 deaths had occurred). Median OS was 22.3 months (95% CI: 18.1, 26.2) in the talazoparib arm and 19.5 months (95% CI: 16.3, 22.4) in the PCT arm with the estimated HR of 0.76 (95% CI: 0.55, 1.06; p=0.1053 [2-sided by stratified log-rank test]).

The new drug application in the US and the marketing authorisation applications in the EU were submitted based on these results and priority review was granted in the US. On 16 October 2018, the FDA approved talazoparib for patients with deleterious or suspected deleterious gBRCAm, HER2-negative locally advanced or metastatic breast cancer. Patients must be selected for therapy based on an FDA-approved companion diagnostic for talazoparib.

1.2.4. The study rationale

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 PK profile of talazoparib as a single agent in Japanese patients with advanced solid tumors. On the amendment 2, this part is called the dose escalation part.

In the global phase 1 (PRP-001), the MTD and recommended 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 the C3441030 study is 0.75 mg/day where no DLT was observed and one level lower than the MTD/RP2D. Talaroparib 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 initial 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 not 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 defined in the Schedule of Activities.

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 will be 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.

Additional information for this compound may be found in the single reference safety document (SRSD), which for the C3441030 study is the investigator's brochure.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. 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/schedule in Japanese patients.	• 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 $t_{½}$, and AUC_{inf} as data permit.
	  • Multiple Dose (MD) (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $C_{ss,\ min}$, $AUC_{ss,\tau}$, 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

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2.2. 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 OR as assessed using RECIST version 1.1 by Investigator Assessment.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To further evaluate anti-tumor activity.	• Objective response (OR) as assessed using RECIST version 1.1 by 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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3. STUDY DESIGN

3.1. Study Overview

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 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.

3.1.1. Starting Dose (Dose Escalation part only)

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

3.1.2. 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 outlined in the Analysis Sets section 9.1 (ie, not evaluable for assessment of DLT) will be replaced. The safety information obtained from the patients who exclude 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.

3.2. 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.

4. PATIENT ELIGIBILITY CRITERIA

The C3441030 study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Dose Escalation part

4.1.1. Inclusion Criteria

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

1. Histological or cytological diagnosis of locally advanced or metastatic solid tumor that is resistant to standard therapy or for which no standard therapy is available.

2. Females and/or male patients age ≥20 years.

3. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

4. Adequate Bone Marrow Function, including:

    a. ANC ≥1,500/mm^3 or ≥1.5×10^9/L without the use of growth factor;

    b. Platelets ≥100,000/mm^3 or ≥100×10^9/L without the use of platelet transfusions or growth factors;

    c. Hemoglobin ≥9 g/dL , with last transfusion at least 14 days prior to the first dose of study treatment.

5. Adequate Renal Function, including:

    a. Estimated creatinine clearance ≥45 mL/min as calculated using the method standard for the institution.

6. Adequate Liver Function, including:

    a. Serum TBili ≤1.5×ULN unless the patient has documented Gilbert syndrome (≤3×ULN for Gilbert syndrome);

    b. AST and ALT ≤2.5×ULN (≤5.0×ULN if there is liver involvement by the tumor);

    c. Alkaline phosphatase ≤2.5×ULN (≤5×ULN in case of bone metastasis).

7. Able to take oral medications.

8. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment.

9. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.

   Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

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

   - Have medically confirmed ovarian failure.

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

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

11. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

4.1.2. Exclusion Criteria

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

1. Patients with known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

2. Major surgery within 4 weeks prior to the first dose of study treatment.

3. Radiation therapy within 4 weeks prior to the first dose of study treatment. Palliative radiotherapy for the treatment of painful bony lesions within 2 weeks prior to the first dose of study treatment.

4. Any anti-tumor systemic cytotoxic therapies within 4 weeks prior to the first dose of study treatment (6 weeks for nitrosoureas or mitomycin-C), treatment with immune modulators (including, but not limited to, corticosteroids (at a prednisone-equivalent

dose of > 10 mg/day), cyclosporine and tacrolimus; locally active treatments such as Beconase are allowed) within 4 weeks prior to the first dose of study treatment.

5. Previous high-dose chemotherapy requiring stem cell rescue.

6. Prior irradiation to >25% of the bone marrow (see Appendix 2 Bone Marrow Reserve in Adults).

7. Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

8. Myocardial infarction within 6 months before starting therapy, symptomatic congestive heart failure (New York Heart Association class III or IV), unstable angina, or unstable cardiac arrhythmia requiring medication. Stable cardiac arrhythmia (e.g. chronic atrial fibrillation controlled by medication) can be eligible.

9. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

10. Participation in other studies involving investigational drug(s) within 4 weeks prior to the first dose of study treatment.

11. Known or suspected hypersensitivity to active ingredient/excipients.

12. Other acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into the study.

13. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

14. Fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for 6 months (180 days) in male patients and 7 months in female patients after the last dose of investigational product.

15. Breastfeeding at screening or at any time during study participation.

16. Current use of a strong P-gp inhibitor (e.g. dronedarone, quinidine, ranolazine, verapamil, itraconazole, ketoconazole), strong P-gp inducer (eg, rifampin, tipranavir, ritonavir), or strong inhibitor of BCRP within 1 week or 5 half lives which ever is

longer prior to the first dose of study treatment.
Patients on verapamil are excluded from the study unless the patient and investigator agree to switch to an alternative, allowed antihypertensive. Any such switch must begin at least 7 days before the first dose of study treatment and additional blood pressure monitoring will be performed as considered medically necessary by the investigator to monitor blood pressure control.

4.2. Expansion part

4.2.1. Inclusion Criteria

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

1. Histologically or cytologically confirmed carcinoma of the breast.

2. Locally advanced breast cancer that is not amenable to curative radiation or surgery and/or metastatic disease.

3. Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation by Myriad Genetics' BRACAnalysis CDx test.

4. No more than 3 prior chemotherapy-inclusive regimens for locally advanced or metastatic disease (no limit on prior hormonal therapies or targeted anti-cancer therapies which mechanistic targets are rapamycin [mTOR] or CDK4/6 inhibitors, immuno-oncology agents, tyrosine kinase inhibitors, or monoclonal antibodies against CTLA4 or VEGF).

5. Prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated.

6. Female and/or male patients age ≥20 years.

7. Have measurable lesion by the RECIST v.1.1.

8. ECOG Performance Status ≤2.

9. Adequate organ function as defined below:

    - Serum AST and ALT ≤2.5 × ULN; if liver function abnormalities are due to hepatic metastasis, then AST and ALT ≤5 × ULN;

    - Total serum bilirubin ≤1.5 × ULN (≤3 × ULN for Gilbert's syndrome);

    - Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis);

    - Estimated creatinine clearance ≥30 mL/min as calculated using the method standard for the institution;

- Hemoglobin ≥9.0 g/dL with last transfusion at least 14 days prior to the first dose of study treatment;
- ANC ≥1500/mm^3 or ≥1.5 x 10^9/L without the use of growth factor;
- Platelet count ≥100,000/mm^3 or ≥100 x 10^9/L without the use of platlet transfusions or growth factor.

10. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment.
11. Able to take oral medications.
12. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.

    Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum FSH level confirming the postmenopausal state;
    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure.

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

13. Evidence of a personally signed and dated ICD indicating that the patient has been informed of all pertinent aspects of the study.
14. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

4.2.2. Exclusion Criteria

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

1. First-line locally advanced or metastatic breast cancer with no prior neoadjuvant and adjuvant chemotherapy unless the investigator determined that treatment with a PARP inhibitor such as talazoparib would be in the best interest of the patient. Note that recurrence within 6 months since the last neoadjuvant or adjuvant treatment can be considered as first-line therapy.
2. Prior treatment with a PARP inhibitor (not including iniparib).

3. Objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease; patients who received platinum in the adjuvant or neoadjuvant setting were eligible; however, patients may not have relapsed within 6 months of the last dose of prior platinum therapy; patients who received low-dose platinum therapy administered in combination with radiation therapy were allowed.
4. Cytotoxic chemotherapy, radiation therapy, antihormonal therapy or other targeted anticancer therapy within 14 days before starting study treatment.
5. HER2 positive breast cancer.
6. Active inflammatory breast cancer (classified as T4d by TNM classification).
7. Central nervous system (CNS) metastases except adequately treated brain metastases documented by baseline CT or MRI scan that had not progressed since previous scans and that did not require corticosteroids (prednisone ≤5 mg/day or equivalent was allowed) for management of CNS symptoms. Patients with leptomeningeal carcinomatosis are excluded.
8. Diagnosis of any other malignancy within 5 years prior to study registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
9. Active and clinically significant bacterial, fungal, or viral infection, including HBV, HCV, known HIV or AIDS-related illness.
10. Participation in other studies involving investigational drug(s) within 14 days before starting study treatment.
11. Major surgery within 14 days before starting study treatment.
12. Myocardial infarction within 6 months before starting study treatment, symptomatic congestive heart failure (New York Heart Association class III or IV), unstable angina, or unstable cardiac arrhythmia requiring medication. Stable cardiac arrhythmia (e.g. chronic atrial fibrillation controlled by medication) can be eligible.
13. Current or anticipated use within 7 days prior to the first dose of study treatment, or anticipated use during the study of strong P-gp inhibitors. For a list of strong P-gp inhibitors, refer to section Section 5.7.
14. Fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 6 months (180 days) in male patients and 7 months in female patients after the last dose of investigational product.
15. Breastfeeding at screening or at any time during study participation (patients who are planning to interrupt breastfeeding are not eligible).
16. Previous high-dose chemotherapy requiring stem cell rescue.
17. Prior irradiation to >25% of the bone marrow (see Appendix 2 Bone Marrow Reserve in Adults).

18. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).
19. Other acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
20. Known or suspected hypersensitivity to active ingredient/excipients.
21. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

4.3. Lifestyle Requirements

In this study, fertile male patients and female patients who are of childbearing potential, as applicable to the study will receive talazoparib, which has been associated with suspected teratogenicity/fetotoxicity. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 6 months (180 days) in male patients and 7 months in female patients after the last dose of talazoparib. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the schedule of activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or partner.

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

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

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

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

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

Male patients must refrain from donating sperm throughout the study and for at least 6 months (180 days) in male patient after the last dose of talazoparib.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation. To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

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

For this study, the investigational product(s) is talazoparib.

5.1. Allocation to Treatment

Dose level allocation for the patients in dose escalation part was performed by the sponsor after patients have given their written informed consent and have completed the necessary baseline assessments.

In all study parts, the site staff will fax or e-mail a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a patient identification number and supply this number to the site. The patient identification number will be used on all study-related documentation at the site.

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

- Confirmation of the patient's enrollment;
- Specification of the dose level for the patient (the dose escalation part only) and;
- Permission to proceed with dosing the patient.

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

5.2. Patient Compliance

Patients will be required to return all unused study treatment at the beginning of each cycle. The number of capsules returned by the patient will be counted, documented, and recorded.

A patient diary will be provided to the patients to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient to include missed or changed talazoparib doses. Patients will be required to return all bottles of talazoparib every cycle. The number of talazoparib capsules remaining will be documented and recorded at each cycle. The patient diary may also be used to support this part of the talazoparib accountability process.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

Talazoparib will be provided as capsules for oral administration. The 0.25 mg capsules will be supplied in separate bottles (or blister cards, as appropriate) and labeled according to local regulatory requirements. For the expansion part, 1.0 mg capsule will also be supplied as a starting dose; 0.25 mg capsule should only be used for patients who require dose reduction.

5.3.2. Preparation and Dispensing

The study treatment should be dispensed at each visit per the schedule of treatment. A qualified staff member will dispense the investigational product in the bottles (or blister cards, as appropriate) provided, in quantities appropriate for the study visit schedule or requirements of dose reduction. The patient/caregiver should be instructed to maintain the product in the bottle (or blister cards, as appropriate) provided throughout the course of dosing, keep the investigational product away from children, and return the bottle (or blister cards, as appropriate) to the site at the next study visit.

5.4. Administration

Talazoparib will be administered on a continuous basis. Talazoparib may be taken with or without food. Before serial PK sampling (ie, on Cycle 1 Day -7 and Cycle 1 Day 22), talazoparib will be administered with plenty of water on an empty stomach ie, patients should refrain from food and beverages (except for water) for at least 6 hours before and 1 hour after dosing.

A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 28 days.

Patients will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing. Patients should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time. If a patient misses a day of treatment, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed. If a patient vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of talazoparib.

5.4.1. Recommended Dose Modifications

Every effort should be made to administer investigational product on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

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

5.4.2. Dosing Interruptions

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in the Dose Delays section.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions section, unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

5.4.3. Dose Delays

This section provides general instructions in case of dose delays. Refer to the Dose Reductions section for adverse events requiring dose reduction at the time of treatment resumption.

In the dose escalation part, re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

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

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

If these conditions are met within 4 weeks of treatment interruption or cycle delay, talazoparib may be resumed. If these conditions are not met, treatment resumption must be delayed up to a maximum of 4 weeks. If patients require discontinuation of talazoparib for more than 28 days at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the Sponsor's medical monitor (See Schedule of Activities, [Dose Escalation Part] footnote e).

If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

5.4.4. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the talazoparib dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity other than renal impairment. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances. In patients with moderate renal impairment (creatinine clearance 30-59 mL/min), the starting dose will be reduced 1 dose level (Table 1).

Dose reduction of talazoparib by 1 and, if needed, 2 dose levels (Table 1) will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 (for 0.75 mg dose level; the dose escalation part only) or 3 (for 1.0 mg dose level) dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and case report form (CRF).

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required.

Table 1. Available Dose Levels

Dose Level	Initial dose of 0.75 mg (Dose Escalation part only)	Initial dose of 1.0 mg
Starting	0.75 mg/day	1.0 mg/day
-1	0.5 mg/day	0.75 mg/day
-2	0.25 mg/day*	0.5 mg/day
-3	NA	0.25 mg/day*

* talazoparib dose de-escalation below 0.25 mg/day is not allowed.

In the dose escalation part, patients experiencing a DLT during Cycle 1 may resume dosing at the next lower dose level (if applicable) once adequate recovery (to baseline or Grade ≤1) is achieved. No dose reductions are planned for patients experiencing toxicities other than those listed as DLTs. However, patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Recommended dose reductions are described in Table 2.

Table 2. Dose Modifications for Investigational Product-Related Toxicity (Dose Escalation part only)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia (hemoglobin < 8.0 g/dL)	Continue at the same dose level.		Withhold dose and monitor weekly until hemoglobin returns to baseline grade. Implement supportive care per local guidelines. Talazoparib may be reduced by 1 dose level. If anemia persists for > 4 weeks without recovery to baseline grade, discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible myelodysplastic syndrome or acute myeloid leukemia.	
Neutropenia (ANC < 1000/μL)	Continue at the same dose level.		Withhold dose and monitor weekly until ANC ≥ 1500/μL. Implement supportive care per local guidelines. Resume talazoparib based on the following recovery times: • ≤ 1 week: The same dose level. • >1 week: Reduce talazoparib by 1 dose level. If neutropenia persists for > 4 weeks without recovery to ≥ 1500/μL, discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible myelodysplastic syndrome or acute myeloid leukemia.	
Thrombocytopenia (platelets < 50,000/μL)	Continue at the same dose level.		Withhold dose until platelets ≥ 75,000/μL. Implement supportive care per local guidelines. Resume talazoparib based on the following recovery times: • ≤ 1 week: The same dose level. • >1 week: Reduce talazoparib by 1 dose level. If thrombocytopenia persists for > 4 weeks without recovery to ≥ 75,000/μL, discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible myelodysplastic syndrome or acute myeloid leukemia.	
Nonhematologic lab abnormality, except liver function tests	Continue at the same dose level.		Withhold dose until toxicity is Grade ≤ 2 (or has returned to baseline for creatinine increases), then resume talazoparib at the same dose or reduce by 1 dose level. Implement supportive care per local guidelines. Contact the sponsor to discuss potential dose modification. Permanently discontinue if lasting >4 weeks, but treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the sponsor.	Withhold dose until toxicity is Grade ≤ 2 (or has returned to baseline for creatinine increases), then resume talazoparib at a 1 dose level reduction. Implement supportive care per local guidelines. Contact the sponsor to discuss potential dose modification. Permanently discontinue if lasting >1 week, but treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the sponsor. Permanently discontinue for recurrence.

Table 2. Dose Modifications for Investigational Product-Related Toxicity (Dose Escalation part only)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Abnormal liver function tests	Continue at the same dose level.		Withhold dose as specified in Table 4 until toxicity is Grade ≤1 or has returned to baseline grade. The investigator and the sponsor should discuss and agree with any decision to rechallenge. Following rechallenge, patients should be closely monitored for signs and symptoms of hepatitis and/or abnormal liver test results. Guidelines for follow-up for possible drug-induced liver injury are provided in Section 8.4.1. Rechallenge should not occur when the liver test abnormalities are accompanied with signs or symptoms consistent with hepatitis or meet severe drug-induced liver injury.	
Nonlaboratory (other toxicities listed above)*	Continue at the same dose level.		Withhold dose until toxicity is Grade ≤ 1 or has returned to baseline, then resume talazoparib at the same dose or reduce by 1 dose level. Implement supportive care per local guidelines. Contact the sponsor to discuss potential dose modification. Permanently discontinue if lasting longer than 4 weeks, but treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the sponsor.	

∗ Talazoparib dose re-escalation may be allowed after the reduced dose is tolerated without recurrence of toxicities, and after discussion with the medical monitor.

Table 3. Dose Modification of Talazoparib Due to Adverse Events (Expansion part only)

Toxicity	Management of Adverse Events
Grade 1 or 2	No requirement for dose interruption or dose reduction.
Grade 3 or 4 Anemia (hemoglobin <8.0 g/dL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to ≥9 g/dL or better, then resume talazoparib at a reduced dose level. If anemia persists for >8 weeks without recovery to at least 9.0 g/dL despite supportive care measures, discontinue talazoparib and refer to a hematologist for evaluation. • Transfusions and erythropoiesis-stimulating agents are permitted to support management of hematological toxicities. (see section 5.7). • If 4 blood transfusions within 3 months period are required, discussion with medical monitor is required to continue/resume study drug.
Grade 3 or 4 Neutropenia (ANC <1000/µL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/µL, then resume talazoparib at a reduced dose level. If neutropenia recurs after the dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/µL, then resume talazoparib at a further reduced dose. If neutropenia persists for >4 weeks without recovery to ≥1500/µL at any dose level despite supportive care measures, discontinue talazoparib and refer to a hematologist for evaluation. • G-CSF and GM-CSF may be used at investigators discretion for the supportive treatment of neutropenia (see Section 5.7).

Table 3. Dose Modification of Talazoparib Due to Adverse Events (Expansion part only)

Toxicity	Management of Adverse Events
Grade 3 or 4 Thrombocytopenia (platelets <50,000/μL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥50,000/μL, then resume talazoparib at a reduced dose. If thrombocytopenia (<50,000/μL) recurs after one dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥75,000/μL, then resume talazoparib at a further reduced dose. If thrombocytopenia persists for >4 weeks without recovery to ≥75,000/μL despite supportive care measures, discontinue talazoparib and refer to a hematologist for evaluation.
Nonhematologic laboratory Grade ≥3 events, except abnormal liver tests	Hold talazoparib as follows: For Grade 3 laboratory abnormalities, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Resume talazoparib at the same dose or reduce by 1 dose level. For Grade 4 laboratory abnormalities, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Resume talazoparib at a 1 dose level reduction. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Talazoparib must be permanently discontinued for unresolved Grade 3 toxicity lasting longer than 14 days or for Grade 4 toxicity lasting longer than 3 days. Treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the sponsor.
Grade ≥3 abnormal liver tests	Hold talazoparib for liver test abnormalities as specified in Table 4. Guidelines for follow-up for possible drug-induced liver injury after the liver test abnormalities resolve to baseline grade are provided in Section 8.4.1. Rechallenge should not occur when the liver test abnormalities are accompanied with signs or symptoms consistent with hepatitis or meet severe drug-induced liver injury.
Nonlaboratory Grade ≥3 events determined to be clinically significant	Hold talazoparib as follows: For Grade 3 adverse events, hold talazoparib until the adverse event resolves to Grade ≤1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level. For Grade 4 adverse events, hold talazoparib until the adverse event resolves to Grade ≤1 or baseline. Resume talazoparib at a reduced dose level.

Abbreviations: ANC=absolute neutrophil count; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor.

Table 4. Criteria for Temporary Withholding of Study Drug in Association With Liver Test Abnormalities

Baseline AST or ALT Value	Elevation
≤3×ULN	>5×ULN (ALT or AST ≥3×ULN with the presence of signs and symptoms consistent with acute hepatitis and/or eosinophilia [≥500 eosinophils/μL])
>3×ULN and ≤5×ULN	>8×ULN
Baseline Total Bilirubin Value	**Elevation**
≤1.5×ULN	>3×ULN
>1.5×ULN and ≤3×ULN (Patients with Gilbert syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation)	>5×ULN

Abbreviations: ALT= alanine aminotransferase; AST= aspartate aminotransferase; ULN= upper limit of normal.

5.5. Investigational Product Storage

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

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

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until the Pfizer provides permission to use the investigational product. It will not be

considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

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

Site staff will instruct patients on the proper storage requirements for take home investigational products.

5.6. Investigational Product Accountability

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

All bottles of study drug and unused study drugs must be returned to the investigator by the patient at the beginning of each cycle and at the end of the trial.

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatment(s)

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions received by patients from screening until the end of study visit will be recorded on the CRF. All concomitant treatments must be approved by the sponsor prior to the first dose of study treatment.

Guidelines for concomitant use of talazoparib with P-gp inhibitors are as follows:

Strong P-gp inhibitors that result in ≥2-fold increase in the exposure of an in vivo probe P-gp substrate according to the University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/) are prohibited: amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar, and verapamil.

Caution and monitoring for potential increased adverse reactions should be used upon concomitant use of the following transporter inhibitors with talazoparib: atorvastatin,

azithromycin, conivaptan, curcumin, cyclosporine, diltiazem, diosmin, eliglustat, elacridar (GF120918), eltrombopag, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis extract.

The list of strong P-gp inhibitors and transporter inhibitors to be used with caution will be updated annually and reflected in the Investigator Brochure.

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

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

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression, after discussion with the Sponsor's medical monitor. In view of the current lack of data about the interaction of talazoparib with radiotherapy, talazoparib treatment should be interrupted during palliative radiotherapy, stopping 10 days before and resuming treatment after recovery from acute radiation toxicities to baseline.

5.7.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

5.7.3. Hematopoietic Growth Factors

In the dose escalation part, primary prophylactic use of granulocyte-colony stimulating factors is not permitted during Cycle 1. They may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines[34]. Refer to the local guideline for the indication and/or administration method of granulocyte colony-stimulating factors (G-CSFs).

5.7.4. Anti-Diarrheal, Anti-Emetic Therapy

In the dose escalation part, primary prophylaxis of diarrhea, nausea and vomiting is not permitted in the first cycle. Primary prophylaxis in subsequent cycles is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatment(s) section.

5.7.5. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatment(s) section.

5.7.6. Corticosteroids

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

5.7.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and talazoparib required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping talazoparib is recommended at least 10 days prior to surgery. Postoperatively, the decision to reinitiate talazoparib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see the Schedule of Activities and Assessments sections. Dose level allocation in the dose escalation part was performed by the sponsor. After patients have given their written informed consent and have completed the necessary baseline assessments, the site staff will fax or e-mail a complete Registration Form to the designated sponsor study team member or designee.

In the expansion part, all patients must have test results of BRACAnalysis CDx indicating deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutations before study treatment. This test will be done as early as possible during the screening period (or outside of 28-days Screening period if patients provide informed concent document (ICD) for BRCA1/2 mutation testing). For patients who already received results from a BRACAnalysis CDx test in 2017 or later, repeat testing is not required but the report must be submitted to Sponsor for approval.

6.2. Study Period

For the treatment period procedures and blood sampling point for PK, see the Schedule of Activities and Assessments sections.

In the dose escalation part, a PK lead-in was undertaken 7 days before Cycle 1 Day 1 to characterize the PK profile. During PK lead-in, Cycle 1 or after completion of Cycle 1, the investigator documented if DLT was observed in each patient. Refer to the Study Manual for details of DLT documentation.

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6.3. Follow-up

For follow-up procedures see the Schedule of Activities and Assessments sections.

In the expansion part, long-term follow-up begins after the last dose and can be conducted by telephone unless follow-up of unresolved AE is required. Survival status and post study therapy can be obtained by any means including telephone, during a visit, chart review, or contact with someone who is knowledgeable of the patient's status (eg, relative, friend, referring healthcare provider).

6.4. Patient Withdrawal

Withdrawal of consent:

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

Lost to follow-up:

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

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the

Withdrawal From the Study Due to Adverse Events (see also the Patient Withdrawal section) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient refuses further visits, no further study-specific evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

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

7.1. Safety Assessment

Safety assessments will include collection of AEs, serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting administration of study treatment-once at the start of screening and once at the baseline visit (immediately before starting the investigational product). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will be repeated at every treatment cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product and from the study.

7.1.2. Adverse Events

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

7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the schedule of activities and analyzed at local laboratories.

Table 5. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Virus Test	Pregnancy Test
Hemoglobin	ALT	Urine dipstick for urine protein: If positive collect 24 hr and microscopic (Reflex Testing) is preferable but urine protein/creatine ratio is also acceptable in agreement with the sponsor	HBV	For female patients of childbearing potential, serum or urine
Platelets	AST		HCV	
White blood cell (WBC)	Alk Phos		HIV	
Neutrophils %	Sodium			
Lymphocytes %	Potassium			
Monocytes %	Magnesium			
Eosinophils %	Chloride			
Basophils %	Total calcium			
Red blood cell (RBC)	Total bilirubin*			
Hematocrit	Blood urea nitrogen (BUN) or Urea			
	Creatinine			
	Uric Acid			
	Glucose (nonfasted**)			
	Albumin			
	Phosphoros or Phosphate			
	Total protein			
	CO_2 (Dose Escalation part only)			

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

** Blood sample might be drawn under fasting conditions on Cycle 1 Day -7 and Cycle 1 Day 22 for the dose escalation part to avoid potential interaction of food on PK assessment although nonfasted sampling is required for Glucose.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination to include weight, vital signs (blood pressure (BP) and pulse rate recorded in sitting position), assessment of ECOG performance status and height; height will be measured at baseline only.

7.1.5. (12-Lead) Electrocardiogram

Electrocardiogram (ECG): A single 12-lead (with a 10-second rhythm strip) tracing will be used. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. If the QTcF is prolonged (>500 msec, ie, CTCAE Grade ≥3), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval to confirm presence of QTc prolongation, then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of > 500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF

interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to 500 msec. Patients will then restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to <500 msec after 2 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate and/or a single ECG(s) may be performed as clinically indicated.

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

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

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.2. Pharmacokinetics Assessments

7.2.1. Plasma for PK analysis of talazoparib

Blood samples (approximately 3 mL) to provide a minimum of approximately 1 mL of plasma for PK analysis will be collected into appropriately labeled tubes containing tripotassium ethylenediaminetetraacetic acid (K_3EDTA) as outlined in the SCHEDULE OF ACTIVITIES section of the protocol. The PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs. In case of QTc values >500 msec, a blood sample for PK analysis should be collected. The date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

Where noted in the schedule of activities, blood samples for talazoparib concentrations will be collected at approximately the same time as other assessments such as pharmacodynamics (PD) samples and ECGs (first ECG then PK collection), etc., wherever possible.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, patient, and sponsor.

With regard to serial PK sampling in lead in phase and on Cycle 1 days 22-23 of the dose escalation part, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

For the expansion part, pre-dose samples obtained within 10% of the nominal time AND collected prior to administration of talazoparib on that day (for pre-dose PK samples) will be considered protocol compliant. Patients must be instructed to withhold their daily dose of study drugs on PK sampling days until the pre-dose PK sample collection has been completed. The actual time of the sample collection and the most recent dosing time before and after each collection will be recorded on the CRF. The date of missing dose should also be recorded in the CRF.

PK samples will be assayed for talazoparib using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

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

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

7.3. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging includes chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Requirement for brain CT or MRI

In the dose escalation part, brain CT or MRI scan for patients with known or suspected brain metastases and bone scan and/or bone x-rays for patients with known or suspected bone metastases are also included Baseline CNS imaging is not required with the exception of symptomatic patients to rule out CNS metastases.

In the expansion part, a brain MRI or CT is to be performed at Screening to evaluate patients for presence/absence of brain metastases. Newly diagnosed CNS metastases at Screening makes a patient ineligible until such time as it can be adequately treated, at which point the

patient may be re-screened. If adequately treated metastatic disease to the brain is present at Screening, an MRI or CT will be performed during the study as clinically indicated. Bone scan will be performed at Screening. If metastatic disease to the bone is present at Screening, a bone scan will be performed every 12 weeks (±7 days) for the initial 24 weeks and every 16 weeks (±7 days) thereafter, and as clinically indicated.

Assessment for anti-tumor activity

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the schedule of activities, whenever disease progression is suspected (eg, symptomatic deterioration), at the time of withdrawal from treatment (if not done in the previous 6 weeks) and at the time of clinical suspicion of disease progression.

Assessment of response will be made using RECIST version 1.1 (see Appendix 3.).

In the expansion part, CR and PR is confirmed by a second image at least 4 weeks from the initial imaging showing response. In addition, BICR will be conducted. All radiographical images for tumor assessment have to be submitted for review. Once study endpoints are summarized and it is notified by Sponsor, tumor assessment including brain and bone scan can be done per local standard practice and the requirement of imaging submission is no longer applicable.

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

7.4. Assessment of germline BRCA mutations for eligibility (Expansion part only)

Patients enrolling in the expansion part are required to have deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutations, identified by BRACAnalysis CDx test. Testing may be performed during the screening period (or outside of the 28-days Screening period for patients who provide their consent for BRCA testing). Results from the BRACAnalysis CDx test may either be obtained through study sponsored central laboratory testing or from results of previously performed BRACAnalysis CDx testing, with Sponsor pre approval. Instructions for submission of blood sample for BRACAnalysis CDx will be provided in the Study Manual.

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8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available

event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

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

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

8.1.1. Additional Details On Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Patient Withdrawal section)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;

- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or

result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;
- Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;

- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

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

8.3. Severity Assessment

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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

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

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

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

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

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

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

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

8.4.2.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

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

8.4.2.3. Occupational Exposure

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

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

8.4.3. Medication Errors

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

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

8.4.3.1. Medication Errors

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

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Analysis Sets

Analysis sets will be defined separately for each study part; the Dose Escalation part and the Expansion part.

1. Safety analysis set

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

2. Full analysis set

   The full analysis set includes all enrolled patients who receive at least one dose of study treatment. By definition, it is identical to the full safety analysis set defined above.

3. Per-protocol analysis set (evaluable for RP2D in the Dose Escalation part only)

   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 first cycle. Patients with major treatment deviations in the first cycle 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

4. PK analysis sets

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

   The PK concentration population is defined as all enrolled patients who are treated and have at least 1 analyte concentration.

9.2. Statistical Methods and Properties

All analyses will be separately conducted for each study part.

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

Table 6. Probability of Escalating Dose

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

The estimated RP2D is the highest tested dose level with DLT rate less than 33% in at least 6 DLT-evaluable patients.

9.3. Sample Size Determination

Dose Escalation part

According to the modified 3+3 design, the number of patients to be enrolled in the study will depend upon the observed safety profile, which will determine the number of patients at each dose level and the number of dose levels explored. It is envisaged that maximum sample size would be 18 patients.

Expansion part

Assuming confirmed talazoparib ORR 50% and null proportion 18.4% based on the results of EMBRACA (Section 1.2.3), 17 patients are needed to preserve 80% probability of the lower limit of two-sided 90% CI of the comfirmed ORR exceeding the null proportion of 18.4%.

Although there are no formal statistical decision rules, if the lower limit of the two-sided 90% CI of confirmed ORR exceeds 18.4%, it is considered that talazoparib shows clinical meaningful antitumor activity in Japanese patients with gBRCAm locally advanced/metastatic breast cancer.

9.4. Efficacy Analysis

Summaries and analyses of efficacy endpoints will include all patients in the Full analysis set.

9.4.1. Analysis of Primary and Secondary Efficacy Endpoints

All analyses for primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumor burden (ie. OR, DC, DoR, PFS) will be performed according to derived Investigator assessment and independent radiology assessment (the expansion part only).

The primary endpoint in the expansion part is the confirmed ORR assessed using RECIST version 1.1 by Investigator Assessment. For the primary analysis, the number, percent and exact two-sided 90% CI will be calculated.

Analyses of the other binary secondary endpoints (e.g. ORR in dose escalation part, ORR assessed by BICR and Disease Control rate (DCR) in the expantion part) will be performed using the same statistical methods as the primary analysis. DCR at 16 and 24 weeks will be provided.

Time-to-event endpoints (e.g. TTR, PFS, DoR and OS) will be descriptively summarized using the Kaplan-Meier method and displayed graphically if appropriate. The 25^{th}, 50^{th}, and 75^{th} percentiles of each endpoint and the 1-year probability of OS will be provided with two-sided 90% CI.

Tumor responseses assessed using RECIST version 1.1 response criteria in Appendix 3, 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 will be listed.

TTR, PFS, DoR and OS will be presented in listings.

Objective Response (OR)

OR is defined as a CR or PR according to the RECIST version 1.1 recorded from first dose of study treatment until disease progression, start of subsequent anti-cancer therapy or death due to any cause.

Disease Control (DC)

DC is defined as CR, PR or SD according to the RECIST version 1.1 recorded in the time period between first dose of study treatment and disease progression or death to any cause.

Time to Tumor 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.

Progression Free Survival (PFS)

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

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.

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.

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.

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[redacted]

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics

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

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, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose, cycle and day.

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 (using a logarithmic scale) 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 20% from the planned time will not be included in summarization.

Expansion part

Trough concentrations will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by cycle and day. Trough concentrations will be plotted for each dose using a box whisker plot by cycle and day. The pre-dose sample should be collected 24 hours ±10% (2 hours and 24 minutes) after the previous day's dose and no more than 5 minutes (0.083 hours) after the administration of the dose on the day of PK sample collection.

9.5.2. 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 CCI [redacted] or significant safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately.

9.6. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set. Baseline value will be defined as the value prior to dosing (either screening or lead-in visit, whichever is closer to the first dose).

9.6.1. Analysis of DLT (the Primary Endpoint for the dose escalation part)

DLT is the primary endpoint of the dose escalation part of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the RP2D as described in the Study Design section. Adverse Events constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints

Adverse Events

AEs will graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades.

Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. Shift tables will be provided to examine the distribution of laboratory toxicities.

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

9.6.3. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data.

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 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 (HR) (QTc) using Fridericia's and Bazett's correction factors. Data will be summarized and listed for RR, PR, QRS, QT, QTc, QTcF and QTcB by starting dose. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute intervals and changes from baseline intervals after treatment by starting dose and time point. For each patient and by starting dose, the maximum change from baseline will be calculated as well as the maximum increase from baseline interval across time-points. Categorical analysis will be conducted for the maximum increase from baseline intervals. Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction methods will be used) using maximum CTCAE Grade.

9.7. Interim Analysis

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, supporting clinical development and/or due to regulatory requests. In addition, in the expansion part, the unblinded reviews may be performed after at least 8 evaluable patients are followed for 12 weeks for the purpose of approaching regulatory authorities to discuss earlier application for approval if promising efficacy is observed (Table 7). The number of promising confirmed objective responders are based on the Bayesian posterior criterion;

Criterion: Posterior Probability (True ORR >18.4% Observed Responders) >99%.

Table 7. Number of Confirmed Objective Responders for Unblinded Reviews

Number of Evaluable Patients	Confirmed Objective Responders (CR+PR) by Investigator and BICR assessment [a]
8 to 9	5
10 to 13	6
14 to 16	7

Abbreviations: BICR = blinded independent central review; CR = complete response; PR = partial response.
a. Minimum number of responders to be met the criterion based on the posterior *Beta* distribution. Prior distribution is *Beta* (½, ½) as non-informative prior.

9.8. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of

Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

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

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

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

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

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. In the dose escalation part, before starting the treatment on Cycle 2 Day 1, the investigator to obtain an additional consent from a patient to continue the study treatment beyond Cycle 1. The investigator will retain the original of each patient's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

End of trial is defined as last patient last visit (LPLV).

14. SPONSOR DISCONTINUATION CRITERIA

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

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 4 weeks. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

PCD is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

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

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Appendix 1. Abbreviations

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

Abbreviation	Term
ADP	adenosine diphosphate
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time curve from zero to infinity
AUC_{last}	area under the plasma concentration-time curve from zero to time of last measurable concentration
AUC_{τ}	area under the plasma concentration-time curve for a dosing interval
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BER	base excision repair
BICR	blinded independent central review
BP	blood pressure
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
C	cycle
C_{max}	maximum concentration
C_{min}	lowest concentration
C1D1	cycle 1 day 1
CI	confidence interval
CK	creatine kinase
CL/F	apparent oral clearance
CNS	central nervous system
CR	complete response
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CT	computed tomography
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
CV	coefficient of variation
DC	disease control

DCR	disease control rate
DDI	drug-drug interaction
DDR	deoxyribonucleic acid damage response
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eg	for example
etc	'and other things' or 'and so forth'
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
gBRCAm	germline breast cancer susceptibility gene mutation
GCP	Good Clinical Practice
G-CSFs	granulocyte colony-stimulating factors
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HR	heart rate
HRD	homologous recombination deficiency
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
ie	that is
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
K_3EDTA	tripotassium ethylenediaminetetraacetic acid
LFT	liver function test
LPLV	last patient last visit

MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NAD	nicotinamide adenine dinucleotide
NCI	National Cancer Institute
OR	objective response
ORR	objective response rate
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PCD	primary completion date
PCT	physician's choice treatment
PD	pharmacodynamics
PD	progression disease
PFS	progression-free survival
P-gp	P-glycoprotein
PgR	progesterone receptor
PI	principal investigator
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	prothrombin time
QD	quaque die
QT	time between the start of the Q wave and the end of the T wave
R_{ac}	accumulation ratio
R_{ss}	linearity ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SD	single dose
SOP	standard operating procedure
SRSD	single reference safety document
$t_{½}$	terminal phase half-life
TBili	total bilirubin
T_{max}	time to maximum concentration
TNBC	triple negative breast cancer
TNM	tumor, node, metastasis

TTR	time to tumor response
ULN	upper limit of normal
US	United States
V_z/F	apparent volume distribution, estimated from terminal phase, for extravascular dosing
WBC	white blood cell

Appendix 2. Bone Marrow Reserve in Adults

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head :			136.6		
	Cranium	165.8	0.75	124.3	13.1	**13.1**
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle :			86.7		
	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs :			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	**10.2**
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
VERTEBRAE	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar) :			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		**1497.7**		**1045.7**	**100.0**	**100.0**

Appendix 3. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING 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 DISEASE

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

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

NORMAL SITES

- Cystic lesions**:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes**:** Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

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

TARGET LESIONS

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

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: WHEN NODAL LESIONS DECREASE TO <10 MM (NORMAL), THE ACTUAL MEASUREMENT SHOULD STILL BE RECORDED.

NON-TARGET DISEASE

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

TARGET DISEASE

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the

sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented, and

  one or more target measurable lesions have not been assessed;

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

  or one or more target lesions cannot be measured accurately (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 DISEASE

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

NEW LESIONS

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

SUPPLEMENTAL INVESTIGATIONS

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

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

SUBJECTIVE PROGRESSION

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

Table 1. Objective Response Status at Each Evaluation

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

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). In the expansion part, for CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR is confirmed by a second image at least 4 weeks from the initial imaging showing response. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

Appendix 4. ECOG Performance Status*

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

*As published in Am J Clin Oncol 5:649-655, 1982.