



**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND PHASE 3 STUDY OF
PD-0332991 (ORAL CDK 4/6 INHIBITOR) PLUS LETROZOLE VERSUS PLACEBO
PLUS LETROZOLE FOR THE TREATMENT OF POSTMENOPAUSAL WOMEN
WITH ER (+), HER2 (-) BREAST CANCER WHO HAVE NOT RECEIVED ANY
PRIOR SYSTEMIC ANTI-CANCER TREATMENT FOR ADVANCED DISEASE**

Compound:	PD-0332991
Compound Name:	Palbociclib
US IND Number:	69,324
European Clinical Trial Database (EudraCT) Number:	2012-004601-27
Protocol Number:	A5481008
Phase:	3

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Document History

Document	Version Date	Summary of Changes
Amendment 7	15 October 2015	<ol style="list-style-type: none"> 1. Protocol Summary/Schedule of Activities/Section 3 Study Design/Section 6.4 Follow-up Visit: Changes reflecting the collection of disease progression dates on subsequent anti-cancer therapies to better understand the potential influence of palbociclib on response to subsequent anti-cancer therapies. 2. Schedule of Activities / Section 5.3.3.1: PD-0332991/Placebo: Language added to clarify that the 7-day off treatment period in any given cycle should always be respected. 3. Schedule of Activities: Editorial changes 4. 1.2.7.7. Rationales for Changes in Amendment 7, 15 October 2015: Provide rationale for changes made in Amendment 7.
Amendment 6	07 April 2015	<ol style="list-style-type: none"> 1. Protocol Summary/Scheduled of Activities/Section 3 Study design/Section 6.4 Follow-up Visit/Section 7.4 Patient Reported Outcomes/Section 9.3.2 Analysis Secondary Endpoints: Changes reflecting the collection of Patient Reported Outcome data during the post-progression follow-up period to assess potential impact of post-progression status on patient's quality of life. 2. Section 1.2.7.6 Rationale for Changes in Amendment 6, 07 April 2015: Provide rationale for changes in Amendment 6. 3. Section 8 Adverse Event Reporting/Section 10 Quality Control and Quality Assurance/Section 15 Publication of Study Results: Editorial changes to reflect current Sponsor's protocol template.
Amendment 5	02 December 2014	<ol style="list-style-type: none"> 1. Study Design/Section 9.6 Interim Analysis: Changed the interim analysis efficacy boundary from O'Brien-Fleming to Haybittle-Peto boundary to ensure that the study would only be stopped at the interim

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Document	Version Date	Summary of Changes
		<p>analysis if the primary analysis (PFS) results are statistically significant, and clinically meaningful.</p> <ol style="list-style-type: none"> 2. Section 1.2.7.5 Rationale for Changes in Amendment 5, 02 December 2014: Added the rationale for changes in Amendment 5. 3. Section 5.4 Drug Storage and Drug Accountability: Editorial changes to reflect current instructions for investigational product destruction at the end of the trial. 4. Section 5.5.1 Prohibited Medications: Strong/Moderate CYP3A inducers/inhibitors and proton-pump inhibitors are allowed for patients who permanently discontinue blinded therapy and continue on study with letrozole monotherapy only. 5. Section 9.3.1 Analysis of Primary Endpoint: Editorial change to clarify planned analyses.
Amendment 4	18 September 2014	<ol style="list-style-type: none"> 1. Schedule of Activities/Section 7.2.1 Laboratory Safety Assessments: Added prospective monitoring of hemoglobin A1c to characterize whether or not palbociclib affects glucose metabolism. 2. Section 1.2.5.4 Ocular Preclinical Data: Updated section to report emergent data findings from the 27-week rat toxicity study suggesting that cataract pathogenesis in rats may be related to altered glucose metabolism. 3. Protocol Summary/Study Design/Section 9.7: updated to reflect Sponsor's decision to no longer require safety review by an internal oncology business unit safety data monitoring committee (IOBU-SDMC) for studies already monitored by an external data monitoring committee (E-DMC). 4. Schedule of Activities/Section 5.3.4.2.2./ Section 6: Language related to cycle delay

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		<p>further defined to clearly state that any new cycle may only start if blinded study treatment can be resumed.</p> <ol style="list-style-type: none"> 5. Section 1.2.5.2: Provided results from study A5481038 designed to investigate the effect of H₂-receptor antagonists, proton pump inhibitors and local antacids on the relative bioavailability of a single oral 125 mg of palbociclib commercial free base hard capsule formulation dose given under fed conditions in healthy volunteers. 6. Section 1.2.7.4 Added the rationale for changes in Amendment 4. 7. Section 5.5: Editorial changes to differentiate between strong and moderate CYP3A inducers/inhibitors. Restriction on CYP3A substrate removed based on updated information indicating that palbociclib is a weak time-dependent inhibitor of CYP3A. Lastly, local antacids and H₂-receptor antagonists were moved under the "Permitted Medications" Section 5.5.3 to reflect results from study A5481038 showing that H₂-receptor antagonists and local antacids given as defined per protocol did not impact the exposure of palbociclib. 8. Section 8.2: Editorial changes to reflect current Sponsor protocol template.
Amendment 3	21 March 2014	<ol style="list-style-type: none"> 1. Schedule of Activities/Section 6 Procedures: Added ophthalmic procedures for all evaluable newly enrolled patients to assess the potential risk of palbociclib-associated crystalline lens changes. 2. Section 1.2.5.4 Ocular Preclinical Data: Included preliminary results from a preclinical ocular study with palbociclib in rats. 3. Section 1.2.7 Amendment Rationale: Section added to provide rationales for each protocol amendment.

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Document	Version Date	Summary of Changes
		<ol style="list-style-type: none"> <li data-bbox="792 300 1409 436">4. Section 3 Study Design: Clarified that safety related assessments must continue if patients continue study treatment beyond RECIST-defined disease progression. <li data-bbox="792 478 1382 615">5. Section 4.4 Sponsor’s Qualified Medical Personnel: Section related to Sponsor’s qualified medical personnel added to align with updated protocol template. <li data-bbox="792 657 1312 762">6. Section 5.3.5 Medication Errors and Overdose: Updated to match updated Protocol template. <li data-bbox="792 804 1398 972">7. Section 7.2.2 Electrocardiogram: Definition of “evaluable” patient revised to ensure that the required number of patients are enrolled in order to appropriately power the analysis in Group 1. <li data-bbox="792 1014 1382 1182">8. Section 7.2.3 Ocular Safety Assessment: Section added to provide details on the ophthalmic procedures to be performed for all newly enrolled, lens grading evaluable patients. <li data-bbox="792 1224 1398 1287">9. Section 8 Adverse Event Reporting: Section updated to reflect current protocol template. <li data-bbox="792 1329 1414 1875">10. Section 9.1 Sample Size Determination: Sample size was revised to account for the possible decrease in palbociclib exposure with concomitant use of proton-pump inhibitors and fasted state prior to Amendment 2. To mitigate the potential impact on the treatment effect in the ITT population an additional 200 patients will be enrolled and required number of PFS events for final analysis will be increased to 347. This will allow the trial to maintain 90% power to detect statistically significant difference assuming a true hazard ratio of 0.69 in favor of the palbociclib plus letrozole arm.

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		<ul style="list-style-type: none"> 11. Section 9.1 Sample Size Determination/ Section 9.6 Interim Analysis: Corresponding to the sample size revision, the final analysis will require 347 PFS events and the Interim Analysis will be performed after approximately 226 PFS events (approximately 65% of total PFS events). 12. Section 15.1 Communication of Results by Pfizer: Updated to match updated Protocol Template. 13. Appendix 6 FACT-B: updated. 14. Appendix 8 Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedure added.
Amendment 2	03 January 2014	<ul style="list-style-type: none"> 1. Clarification of inclusion criterion #10 to emphasize the importance of collecting recurrent/metastatic tissue whenever possible. 2. Clarification of exclusion criterion #1 to highlight the need to confirm HER2 status on the most recent tumor sample whenever possible. 3. Clarification of inclusion criterion #4 to clarify that patients with FSH/estradiol blood levels within the post-menopausal range may be eligible. 4. Clarification of exclusion criterion #17 to only exclude patient participating in the active treatment phase of other interventional trials within the protocol defined period. 5. Section 1.2.5.2 – Added preliminary results from two clinical pharmacology studies supporting revisions of Sections 5.3.3, 5.5.1, and 5.5.2. 6. Section 5.3.3 - Added recommendation to take palbociclib with a meal instead of under minimal fasting conditions.

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Document	Version Date	Summary of Changes
		<ul style="list-style-type: none"> 7. Section 5.5.1 - Added prohibition to take proton-pump inhibitors while receiving study drugs. 8. Section 5.5.2 - Added recommendation to use local antacids as well as H₂-receptor antagonist as alternative treatment for patients requiring gastroprotective treatment. 9. Editorial changes to address typo and align protocol language with clarified criteria.
Amendment 1	01 October 2013	<ul style="list-style-type: none"> 1. For France only: Clarification of inclusion criterion #10 in Section 4.1 “Inclusion Criteria” to emphasize that every effort should be made to collect tissue sample from the recurrent/metastatic tumor at baseline at the request of the competent authority in France: Agence Nationale de Sécurité du Médicament (ANSM).
Original protocol	30 October 2012	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/external review boards (IRBs)/ (ERB), etc.

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PROTOCOL SUMMARY

Indication:

Estrogen receptor-positive (ER(+)), HER2-negative (HER2(-)) Advanced Breast Cancer (ABC).

Background and Rationale:

Breast cancer (BC) is the most common invasive cancer in women, with more than one million cases and over 411,000 deaths occurring worldwide annually. Although age-adjusted mortality from breast cancer has been decreasing since 1990, the median survival for patients with metastatic disease is still only approximately 18-24 months and the medical need for more active agents in this clinical setting remains very high.

The role of estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormonal receptor positive advanced breast cancer, particularly for those with slowly progressive disease and limited tumor-related symptoms. Letrozole (Femara[®]) is an oral nonsteroidal aromatase inhibitor approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer (ABC).

PD-0332991 (palbociclib) is an oral cyclin-dependent kinase (CDK) 4/6 inhibitor that has been under investigation in Phase 1 and 2 clinical trials in multiple indications. PD-0332991 prevents cell cycle progression from G1 to S phase and has shown antitumor activity in multiple preclinical models, including in estrogen receptor-positive (ER+) luminal breast cancer cell lines.

Furthermore, pre-clinical exploration using a breast cancer cell line panel has demonstrated presence of retinoblastoma (Rb) protein and upregulation of cyclin D1 as well as decreased CDKN2A (p16) that were associated with sensitivity to PD-0332991 as well as with its effects upon cell cycle and growth inhibition. These gene expression findings were also associated with the luminal subtype versus basal-like subtype of BC.

These results, together with published data on the interaction of estrogens and CDKs and the important role of cell cycle-related proteins in the genesis and maintenance of breast cancer, led to the initiation of a randomized Phase 2 clinical trial (A5481003) investigating the antitumor activity of PD-0332991 in combination with letrozole and single-agent letrozole in the first-line treatment of ER(+)/HER2(-) ABC patients. The Phase 2 study was divided into 2 parts. In Part 1, patient selection was based only on ER/HER2 status while in Part 2, patients were additionally prospectively selected taking into account tumor CCND1 amplification and/or CDKN2A (p16) loss.

After a median follow-up of 16.5 months, preliminary results from Part 1 of this Phase 2 trial suggest that the combination of PD-0332991 with letrozole is superior to letrozole alone in the selected patient population as demonstrated by prolonged progression-free survival (median 18.2 months vs 5.7 months, respectively), and improved objective response and disease control rates (52% vs 32% and 76% vs 47%, respectively) in patients treated with the combination. Results from the Phase 2 Part 2 are not yet mature.

The combination therapy was generally well tolerated when compared to letrozole alone with AEs similar to those seen with PD-0332991 and letrozole when administered alone. Uncomplicated neutropenia, leucopenia, and fatigue were the most frequent adverse events, and the most commonly reported Grade 3 treatment-related adverse events were neutropenia (54%) and leucopenia (21%) in patients treated with the combination therapy. Grade 4 events included neutropenia and fatigue each reported for 6% of patients treated with PD-0332991 + letrozole. No Grade 4 events were reported in the letrozole alone arm. Treatment-related Grade 1/2 AEs reported more frequently in patients in the PD-0332991 + letrozole arm compared with the letrozole alone arm included leukopenia, anemia, fatigue, alopecia, arthralgia, nausea, neutropenia, and thrombocytopenia. Hot flush was the most common Grade 1/2 treatment-related AE reported in patients enrolled in the letrozole alone arm.

Overall, 3 (9%) patients in the PD-0332991 + letrozole arm and 1 (3%) patient in the letrozole alone arm discontinued the Phase 2 Part 1 of Study A5481003 due to AEs including 1 patient with Grade 4 fatigue (not related to PD-0332991) and 2 patients with Grade 3 neutropenia in the PD-0332991 + letrozole arm and 1 patient with Grade 2 nausea in the letrozole alone arm. The median duration of treatment was 13.7 months in the PD-0332991 + letrozole arm vs 5.4 months in the letrozole alone arm, with PD-0332991 dosing interruptions and dose reductions due to AEs reported in 61% and 39% of patients enrolled in the PD-0332991 + letrozole arm respectively. The median duration of dosing interruptions was 4.5 days, and the median time to first dosing interruption was 55.5 days. Despite the dosing interruptions and dose reductions, the median dose intensity for PD-0332991 was 87% across all cycles.

This randomized Phase 3 Study (A5481008) provides the opportunity to confirm the clinical benefit of the combination of PD-0332991 with letrozole observed in the randomized Phase 2 study. This study is designed to demonstrate that the combination of PD-0332991 with letrozole provides superior clinical benefit compared to letrozole in combination with placebo in postmenopausal women with ER(+)/HER2(-) ABC who have not received any prior systemic anti-cancer therapies for their advanced disease.

Objectives:

Primary Objective:

- To demonstrate that the combination of PD-0332991 with letrozole is superior to placebo plus letrozole in prolonging progression-free survival (PFS) in postmenopausal women with ER(+)/HER2(-) advanced breast cancer who have not received any prior systemic anti-cancer therapies for their advanced disease.

Secondary Objectives:

- To compare measures of tumor control duration and overall survival between the treatment arms;
- To compare safety and tolerability between the treatment arms;
- To compare health-related quality of life between the treatment arms;
- To characterize the effects of PD-0332991 at therapeutic doses in combination with letrozole on QT interval in this patient population;
- To determine trough PD-0332991 plasma concentration in this patient population and explore the correlations between exposure and response and/or safety findings;
- To characterize alterations in genes, proteins, and ribonucleic acids (RNAs) relevant to the cell cycle (eg, CCND1 amplification, CDKN2A deletion), drug targets (eg, CDK 4/6), and tumor sensitivity and/or resistance (eg, Ki67, pRb) in tumor tissues.

Study Design:

This is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trial comparing the efficacy and safety of PD-0332991 in combination with letrozole versus placebo plus letrozole in postmenopausal women with ER(+)/HER2(-) ABC. Eligible patients will have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease and will be candidates to receive letrozole as first-line treatment for their advanced disease. In order to avoid inclusion of patients who are refractory or resistant to non-steroidal aromatase inhibitors, patients who received anastrozole or letrozole as a component of their (neo)adjuvant regimen may only enter the study if their disease did not progress while on or within 12 months from completion of their anastrozole/letrozole-containing (neo)adjuvant therapy. Patients will not have received any prior systemic anti-cancer therapies for their advanced disease and will not be candidates for curative therapies. Patients must have measurable disease as per RECIST v.1.1 or bone disease as their only site of disease. Tumor tissue availability is required for patient participation. At least 650 patients will be randomized 2:1 between the experimental arm (Arm A: at least 433 patients treated with PD-0332991 plus letrozole) and the control arm (Arm B: at least 217 patients treated with placebo plus letrozole).

Patients will be stratified by site of disease (visceral vs non-visceral), by disease-free interval since completion of prior (neo)adjuvant therapy (de novo metastatic; ≤ 12 months; >12 months) and by the nature of prior (neo)adjuvant anti-cancer treatment received (prior hormonal therapy; no prior hormonal therapy).

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Patients randomized to Arm A (experimental arm) will receive:

- PD-0332991, 125 mg, orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

in combination with

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients randomized to Arm B (control arm) will receive:

- Placebo orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

in combination with

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients will continue to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. However, patients may continue treatment as assigned at randomization beyond the time of RECIST-defined disease progression at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anti-cancer treatment is initiated. In this case, the patient would continue with routine safety assessments as per the [Schedule of Activities](#) for the active treatment period.

The importance of timely and complete disease assessments in this study cannot be overstated. Disease assessments will be performed every 12 weeks (± 7 days) from the date of randomization. Patients with bone lesions identified at baseline will also have repeat bone scans performed every 24 weeks (± 7 days) from the date of randomization. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anti-cancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. A series of incomplete disease assessments will result in censoring of the primary endpoint of PFS back to the time of the last full assessment that did not show disease progression. Off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial and must be avoided wherever possible.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1 will continue to have tumor assessment performed during the follow-up visits every

12 weeks (± 7 days) and bone scans (as applicable) every 24 weeks (± 7 days) until RECIST-defined disease progression, initiation of new anti-cancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

Patients discontinuing the active treatment phase will enter a follow-up period during which Functional Assessment of Cancer Therapy – Breast (FACT-B), survival and new anti-cancer therapy information (including regimen number, name of therapy, start/stop dates, and dates of disease progression on subsequent anti-cancer therapies) will be collected every 6 months from the last dose of investigational product. The follow-up period will conclude at the time of the final OS analysis. Crossover will not be allowed in the trial.

Efficacy analyses will be performed using the local radiologist's/investigator's tumor assessments as the primary data source. However, a blinded independent third-party core imaging laboratory will complete a retrospective review of radiographic images and clinical information collected on-study to verify the protocol-defined endpoints of disease response and progression determinations as assessed by the investigator.

An independent third party External Data Monitoring Committee (E-DMC) will monitor the safety data on a periodic basis. The E-DMC will make recommendation as to whether the trial should continue based on ongoing reviews of safety data. The E-DMC will also evaluate efficacy at the interim analyses and make a recommendation regarding study continuation based on observed results of the study. The E-DMC membership and governance is outlined in a separate charter.

Endpoints:

Primary Endpoint

- Progression-Free Survival (PFS).

Secondary Endpoint(s)

- Overall Survival (OS);
- 1-year, 2-year, and 3-year Survival Probabilities;
- Objective Response (OR: Complete Response or Partial Response);
- Duration of Response (DR);
- Disease Control (DC: CR + PR + Stable disease ≥ 24 weeks);
- Corrected QT interval (QTc);
- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1, CDKN2A), proteins (eg, Ki67, pRb), and RNA expression (eg, cdk4, cdk6);

- Trough plasma concentration of PD-0332991;
- EuroQol (EQ-5D) Score (see [Appendix 5](#));
- Functional Assessment of Cancer Therapy - Breast (FACT-B) (See [Appendix 6](#));
- Type, incidence, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.0), seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.

Statistical Methods:

The primary purpose of this study is to demonstrate that the combination of PD-0332991 with letrozole is superior to placebo plus letrozole in prolonging PFS in postmenopausal women with ER (+), HER2 (-) ABC who have not received any prior systemic anti-cancer treatment for advanced disease. All primary and secondary endpoints based on radiological (and photographic where applicable) assessments of tumor burden (ie PFS, OR, DR, DC) will be derived using the local radiologist's/investigator's assessment. Tumor assessments will also be performed in retrospective by a blinded independent third-party core imaging laboratory and the data will be used for secondary supportive analyses. The study is designed to test the null hypothesis that the true PFS distributions for both PD-0332991 plus letrozole and placebo plus letrozole arms are the same with a median PFS of 9 months versus the alternative hypothesis that the true PFS distribution has a median that is longer than 9 months for the PD-0332991 plus letrozole arm.

The sample size for this study is determined based on the assumptions that the median PFS for ABC patients receiving placebo plus letrozole in the first-line treatment setting is 9 months and a risk reduction by 31% (hazard ratio of 0.69) or an improvement by 44% to a median PFS of 13 months in the PD-0332991 plus letrozole treatment arm is clinically meaningful. A total of 347 events are required in the 2 arms of the study based on a 2:1 randomization to have 90% power to detect a difference assuming a true hazard ratio of 0.69 in favor of the PD-0332991 plus letrozole arm using a one-sided log-rank test at a significance level of 0.025. Assuming a 15% drop-out rate on either treatment arm, a non-uniform accrual accomplished over a 15-month period and follow-up that will continue for about 10 months after the last patient is enrolled, a total sample size of approximately 650 patients (approximately 433 patients in the PD-0332991 plus letrozole arm and approximately 217 patients in the placebo plus letrozole arm) is required.

The sample size described above will also allow the assessment of differences in the secondary endpoint of overall survival (OS) with a high level of significance. The OS outcome of a Phase 3 clinical trial in a similar patient population demonstrated a median OS of 34 months for the arm receiving letrozole. Using this value as an assumption with a hypothesized 26% risk reduction (a hazard ratio of 0.74) or 35% improvement in median OS (from 34 months to 46 months) in patients randomized to receive PD-0332991 plus letrozole and a follow-up period of approximately 68 months, evaluation of 390 events using a

one-sided log-rank test is required for a significance level of 0.025 and power of 80% to detect a difference. OS will be hierarchically tested for significance at its interim analysis, provided the primary endpoint, PFS, is statistically significant at the interim PFS analysis, or at the final PFS analysis.

Descriptive statistics will be used to summarize all patient characteristics, treatment administration, investigational drug compliance, efficacy endpoints, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate.

The primary efficacy analyses will be based on the *intent-to-treat* (ITT) population, defined as all patients randomized to the study. Some efficacy analyses will also be performed on the *as-treated* (AT) population, defined as patients who receive at least 1 dose of study treatment (ie, PD-0332991/placebo or letrozole), with treatment assignments designated according to actual study treatment received.

Time-to-event endpoints, including PFS, DR, and OS will be summarized using Kaplan-Meier methods and displayed graphically. The median event time and 2 sided 95% confidence interval for the median will be provided for each endpoint. Stratified log rank tests will be used to compare PFS and OS between the treatment arms.

The 1-year, 2-year, and 3-year survival probabilities will be estimated using the Kaplan-Meier method and a 2 sided 95% confidence interval for the log $[-\log(1\text{-year, 2-year or 3-year survival probability})]$ will be calculated using a normal approximation using the Greenwood's formula and then back transformed to give a confidence interval for the 1-year, 2-year, and 3-year survival probability itself.

The objective response rate (ORR) will be summarized by treatment arm along with the corresponding exact 2 sided 95% confidence interval calculated using a method based on the F distribution. Response rate comparisons between the 2 treatment arms as randomized will be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis.

The study is designed to have one interim analysis and the final analysis based on the primary endpoint of PFS. A formal efficacy stopping boundary (Haybittle-Peto) for rejecting the null hypothesis will be used for the interim analysis. The purposes for the interim analysis are to allow early stopping of the study for futility or efficacy, to assess safety of the combination regimen, and to potentially adjust the sample size. The interim analysis will be performed after approximately 226 patients have documented progressive disease or die (approximately 65% of the total events expected). If the value of the test statistic exceeds the Haybittle-Peto efficacy boundary ($z \geq 4.2059$, $p \leq 0.000013$), the trial may be stopped for efficacy. Under exponential distribution assumption, this boundary equates to a hazard ratio of ~ 0.55 or smaller in favor of the palbociclib plus letrozole arm versus the letrozole alone arm. Alternatively, as appropriate, the sample size of the study may be adjusted using the method outlined by Cui et al. If the results of the interim analysis indicate serious safety concerns, the sponsor will communicate with the Health Authorities regarding stopping the clinical trial.

An interim analysis for efficacy is also planned for the secondary endpoint of OS. The analysis will be performed at the time of the interim or final PFS analyses if the primary endpoint PFS analysis is positive. The nominal significance levels for the interim and final analyses for OS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule. The overall significance level for the efficacy analysis of OS will be preserved at 0.025 (one-sided test).

OS will be hierarchically tested for significance at the time of PFS analyses, provided the primary endpoint, PFS, is statistically positive at the interim or final PFS analyses. If OS does not yield a significant result at these analyses, OS will be tested at the final OS analysis. If PFS is not significant at the interim and/or final PFS analyses, OS will not be statistically evaluated.

All patients treated with at least one dose of study treatment (ie, PD-0332991/placebo or letrozole) will be included in all safety analyses. Summaries of AEs and other safety parameters will be provided as appropriate. Frequencies of patients experiencing at least one AE will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, severity, relationship to study drug, action taken, and clinical outcome. Severity of the AEs will be graded according to the NCI CTCAE version 4.0. Summary tables of clinical laboratory results will be prepared to examine the worst toxicity grade on study and distribution of laboratory measures over time. Shift tables will be provided to examine the distribution of laboratory abnormalities.

Breast cancer-specific quality of life mean scores at each assessment time point and change from baseline scores will be compared between the treatment arms at various time points using a mixed model repeated measures (MMRM) approach adjusting for specified covariates. In addition, analyses will be performed to determine if the change from baseline scores achieve the appropriate minimally important difference (MID) cut-off for the scale being examined. Patients from the ITT population who completed a baseline assessment and at least one post-baseline assessment prior to study treatment discontinuation will be considered evaluable for the patient-reported outcome (PRO) analysis. In addition to the above analyses, an examination of the time to deterioration (TTD) also will be carried out using survival analysis methods. A composite definition for deterioration based on death, tumor progression, and MID will be used.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures ([Section 6](#)) and Assessments ([Section 7](#)) for detailed information on each procedure and assessment required for compliance with the protocol.

A5481008 Schedule of Activities

Protocol Activity	Screening	Active Treatment Phase ^a - One Cycle = 28 days			End of Treatment / Withdrawal ^c	Post-Treatment Follow-Up ^d
		Cycles 1 and 2		Cycles ≥ 3		
		Day 1 ^{b,v}	Day 14	Day 1 ^v		
Study Day	Within 28 days prior to randomization unless specified otherwise	$\pm 2d$	$\pm 2d$	$\pm 2d$		
Time Window						$\pm 7d$
Baseline Documentation						
Informed Consent Process ^e	X					
Medical / Oncological History ^f	X					
Baseline Signs / Symptoms		X ^g				
Retained Pharmacogenomic Blood Sample ^h		X				
Tumor Tissue for Biomarker ⁱ	X				X ⁱ	
Physical Examination/Vital signs ^j	X	X ^b		X	X	
Ophthalmic Examination ^k	X			X	X	
ECOG Performance Status	X	X		X	X	
Laboratory Studies						
Hematology ^l	X	X ^b	X	X	X	
Blood Chemistry ^l	X	X ^b	X	X	X	
12-Lead ECG ^m	X ^m	X ^b	X ^m	X ⁿ	X	
Disease Assessment						
Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease ^o	X	◀--▶ ^{p,o} Performed every 12 weeks (± 7 days) from the date of randomization			X	X ^o

Protocol Activity	Screening	Active Treatment Phase ^a - One Cycle = 28 days			End of Treatment / Withdrawal ^c	Post-Treatment Follow-Up ^d
		Cycles 1 and 2		Cycles ≥3		
		Day 1 ^{b, v}	Day 14	Day 1 ^v		
Study Day Time Window	Within 28 days prior to randomization unless specified otherwise	±2d	±2d	±2d		±7d
Radionuclide Bone Scan, Whole Body ^o	X	◀--▶ ^{q, o} Performed every 24 weeks (±7 days) from the date of randomization			X	X ^o
Other Clinical Assessments						
Drug Compliance ^f		◀--▶				
Averse Event Reporting ^s	X	X	X	X	X	X
Review Concomitant Medications/Treatments ^t	X	X	X	X	X	X
EuroQol; EQ-5D ^u		X		X	X	
FACT - Breast Questionnaire ^u		X ^u		X	X	X ^y
Survival Follow-up						X
Study Treatment						
Randomization	X					
Letrozole (both treatment arms)		Once Daily ▶--▶ ^w				
PD-0332991 or Placebo		◀--▶ ^x Once Daily on Day 1 to Day 21 of each cycle followed by 7 days off				
Special Laboratory Studies						
Pharmacokinetics ^m			X			

- Active Treatment Phase:** All assessments should be performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. For the purposes of this trial 1 cycle is 28 days. A cycle could be longer than 28 days if persistent toxicity delays the initiation of the subsequent cycle.
- Cycle 1/Day 1:** Blood chemistry, hematology, 12-lead ECG and physical examination not required if acceptable screening assessment is performed within 7 days prior to randomization.
- End of Treatment/Withdrawal:** End of Treatment/Withdrawal evaluations will be performed as soon as possible but no later than 4 weeks (ie, 28 days) ±7days from last dose of study treatment and prior to the initiation of any new anti-cancer therapy. Obtain these assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks for disease assessments).

- d. **Post Treatment Follow-up:** After discontinuation of study treatment, post-treatment follow-up information (ie, survival status, and post-study anti-cancer therapy details [including regimen number, name of therapy, start/stop dates, and dates of disease progression on subsequent anti-cancer therapies]) will be collected every 6 months (± 7 days) from the last dose of study treatment. Telephone contact is acceptable.
- e. **Informed Consent:** Informed consent may be obtained greater than 28 days from randomization; however, must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in [Section 6.1](#)).
- f. **Medical/Oncological History:** To include information on prior anti-cancer treatments.
- g. **Baseline Signs/Symptoms:** Baseline tumor related signs and symptoms will be recorded at the Cycle 1 Day 1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
- h. **Retained Pharmacogenomic Blood Sample:** A single 4 mL blood sample (Prep D1; K2 EDTA whole blood collection optimized for DNA analysis) will be collected pre-dose at the Cycle 1 Day 1 visit from all patients, unless prohibited by local regulations, to be retained for possible analysis of genetic associations with pharmacokinetics, drug response or adverse drug reactions. Examples of genes that may affect pharmacokinetics or drug response include, but may not be limited to, genes encoding drug metabolizing enzymes and transporters, and genes thought to be related to the mechanism of drug action.
- i. **Mandatory Tumor Tissue For Confirmatory Testing and for Biomarker Assessments:** Tumor tissue is required for patient participation. Submission of formalin-fixed paraffin embedded (FFPE) tumor samples (blocks) of adequate size to allow for three 0.6 mm diameter x 5 mm deep core punches that will be used to generate a tissue microarray are needed. If FFPE tissue block cannot be submitted, at least 12 glass slides, each containing an unstained 5-micron FFPE tissue section, will be required for patient participation. Tissue sample from a metastatic or recurrent tumor lesion must be provided whenever possible. If such tissue sample is unavailable, a *de novo* fresh biopsy is recommended when, in the investigator's judgment, such biopsy is feasible and can be safely performed. A sample of the original diagnostic tissue (ie, archival) will also be collected when available and sent to the sponsor-designated central laboratories for assessment of biomarkers associated with sensitivity and/or resistance to PD-0332991 (eg, Ki67, CDKN2A (p16), pRb). Retrospective confirmation of ER status and prospective confirmation of HER2 status when required to be repeated for eligibility purpose will be performed using the most recent tumor sample. Original diagnostic tumor tissue will be used for confirmation of ER and HER2 status in the event that a recurrent/metastatic tissue sample is not available and a fresh biopsy of the recurrent/metastatic lesion is not feasible. An optional fresh tumor biopsy will be collected at the end of treatment visit, only for patients who discontinue treatment due to disease progression. The tumor tissue will be used to determine possible mechanisms of resistance. Tissue samples from all patients will be used for additional biomarker analyses. Details on preparation of these samples including processing, storage, and shipment will be provided in the Study Manual.
- j. **Physical Examination/Vital signs:** A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening and, Day 1 of Cycles 1 and 2. Symptom-directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.
- k. **Ophthalmic Examinations:** Once Amendment #3 is IRB approved, all newly enrolled patients will undergo an ophthalmic examination at baseline, and on study treatment after 3 months (Cycle 4 Day 1), 6 months (Cycle 7 Day 1), 12 months (Cycle 13 Day 1), every 12 months (Day 1 of Cycles 25, 37 etc...) thereafter, and at the End of Treatment visit. Additional ophthalmic examinations may be performed during the study as clinically indicated (including for patients randomized prior to Amendment 3 approval). The ophthalmic examinations will include: best corrected distant visual acuity (Snellen), refractive error associated with best corrected distant visual acuity, intraocular pressure (IOP – one reading), slit lamp biomicroscopy of the anterior segment including cell count and flare grading, crystalline lens grading using the Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading procedure, and fundoscopy. All ophthalmic examinations will be performed by an ophthalmologist. Refer to [Section 7.2.3](#). Ocular Safety Assessments for further details on these procedures.
- l. **Hematology, and Blood Chemistry Panel:** Hematology includes hemoglobin, WBC, absolute neutrophils, platelet count. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, BUN (or urea), serum creatinine, and albumin. Additional

- hematology/chemistries panels may be performed as clinically indicated. Additionally, hemoglobin A1c will be measured during the active treatment phase in all patients every 3 months from the date of randomization (ie, C4D1, C7D1, C10D1, etc), and at the end of treatment visit.
- m. **12-Lead ECG/Pharmacokinetics:** Refer to [Pharmacokinetic and ECGs Schedule of Activities](#) table for details and timing of procedures.
 - n. **12-Lead ECG:** To be performed on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 will be performed as clinically indicated. Refer to [Pharmacokinetic and ECGs Schedule of Activities](#) table for further details and timing of procedures.
 - o. **Disease Assessments:** Please refer to the [tumor assessment requirement flowchart](#) for details and timing of procedures.
 - p. CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; clinical evaluation of superficial disease: Please refer to the [tumor assessment requirement flowchart](#) for details and timing of procedures.
 - q. **Radionuclide Bone Scan, Whole Body:** Please refer to the [tumor assessment requirement flowchart](#) for details and timing of procedures.
 - r. **Drug Compliance:** PD-0332991, placebo and letrozole bottle(s)/blisters including any unused capsules/tablets will be returned to the clinic for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.
 - s. **Adverse Events:** For SAEs, the active reporting period begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. Following the active safety reporting period, other SAEs of which the investigator becomes aware should be reported to Pfizer, unless the SAE is attributed by the investigator to complications of either the underlying malignancy or any subsequent anti-cancer therapy or to the patient's participation in a subsequent clinical study. AEs (serious and non serious) should be recorded on the CRF from the time the patient has taken at least one dose of study treatment through last patient visit.
 - t. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment.
 - u. **EQ-5D, FACT-B Assessments:** Patients will complete questionnaires prior to any study or medical procedure on Day 1 of Cycles 1, 2 and 3 and then Day 1 of every other cycle thereafter starting with Cycle 5 (ie, Cycle 5, 7, 9, etc), and at the end of treatment visit. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. Interviewer administration in clinic may be used under special circumstances.
 - v. **Cycle X, Day 1:** In the event that the start of a new cycle is delayed due to treatment related toxicity, procedures required on Day 1 of the given cycle will be performed when PD-0332991/placebo is resumed. New cycle Day 1 procedures (ie, physical examination, ECOG performance status, ECG, Quality of Life questionnaires, blood chemistry, hematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.
 - w. **Letrozole (both treatment arms):** To be taken orally, daily, and continuously.
 - x. **PD-0332991 or Placebo:** To be taken orally, daily from Day 1 to Day 21 (21 days) of every 28-day cycle followed by 7 days off treatment. In the event the Day 1 clinic visit of the subsequent cycle is scheduled during the -2 day allowable visit time window (ie. Day 27, Day 28), patients must be instructed to complete their 7-day off treatment period of the current cycle prior to resuming blinded therapy even if criteria for treatment resumption are met at the visit. Cycle off treatment periods of less than 7 days are considered protocol deviations.
 - y. **FACT-B Assessments:** After patients discontinue from the active treatment phase, FACT-B questionnaire will continue to be collected during the follow-up period every 6 months (+/- 7 days) from the last dose of investigational product until patient permanent discontinuation from study or end of follow-up period whichever occurs first. During the follow-up period, all self-assessment questionnaires should preferably be completed by the patients during a scheduled clinic visit. However, if no clinic visits are being scheduled during the follow-up period interviewer administration via phone call may be used instead and documented accordingly in the patient source notes.

Pharmacokinetic and ECGs, Schedule of Activities															
Protocol Activity	Screening						Active Treatment Phase								End of Treatment
	Within 28 days prior to randomization unless specified otherwise						Cycle 1				Cycle 2	Cycle ≥ 4			
	Day -27 to Day 0	Day 0 (day prior to Day 1)					Day 1	Day 14				Day 14	Day 1		
	ECG _E [*]	ECG1 ^o	2 Hrs Post-ECG1	4 Hrs Post-ECG1	6 Hrs Post-ECG1	8 Hrs Post-ECG1	0 Hrs Pre-dose	0 Hrs Pre-dose	2 Hrs Post-dose	4 Hrs Post-dose	6 Hrs Post-dose	8 Hrs Post-dose	0 Hrs Pre-dose	0 Hrs Pre-Dose	Anytime
Group 1 (approx. 60 Patients) at selected sites															
12 Lead ECG ^a	X	X	X	X	X	X	X ^a	X	X	X	X	X	X	X	X
Pharmacokinetics ^b								X	X	X	X	X	X		
Group 2 (All other patients)															
12 Lead ECG ^a	X						X ^a	X					X	X	X
Pharmacokinetics ^b								X					X		

*ECG_E = Triplicate ECGs performed to determine patient’s eligibility.
^oECG1 = First triplicate ECGs performed for patient in Group 1.

- a. **12-lead ECG:** A 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. ECGs will be performed in triplicate approximately 2 minutes apart but within 10 minutes for all 3 ECGs. It is preferable that the machine used has the capacity to calculate the standard intervals automatically. ECG interval readings by the ECG recorder’s algorithm will be read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents. Blinded manual interval measurements at a core ECG laboratory will be used for primary statistical analysis of ECG data in group 1 patients (as described below). ECG measurements will include PR interval, QT interval, RR interval and QRS complex. Additional ECGs may be performed as clinically indicated.

Triplicate ECGs (also referred as ECG_E) will be performed during the screening period for all patients to determine the mean QTc interval for eligibility purpose.

Patients found to be eligible will be part of one of the two groups highlighted below depending on which site screened the patient. ECG frequency for each group is described below:

Group 1 (approximately 60 patients) at selected sites:

- On the day preceding treatment initiation (day 0), triplicate ECGs will be obtained at time 0 (first ECG also referred to as ECG1), and then 2, 4, 6, and 8 hours after ECG1.
- At Cycle 1 Day 14, triplicate ECGs will be obtained at 0 hour (pre-dose) and then, 2, 4, 6, and 8 hours following PD-0332991/placebo dosing. Timing of ECGs performed on Day 14 MUST be time-matched (clock time +/- 35 minutes) with ECG assessments performed on Day 0 (eg, if ECG1 on Day 0 was performed at 10:00 AM then the 0 hour triplicate ECGs on Day 14 must be performed within the 9:30AM-10:30AM timeframe but as close as possible to 10:00AM whenever feasible). On day 14 of Cycle 1, study treatment should be administered immediately after the pre-dose PK draw has been collected.

All ECGs should be obtained after a fast of at least 1 hour. ECGs should be performed immediately before PK blood draws at respective time points. Patients who cannot complete ECG measurements on Day 0 and/or PK-matched ECG measurements (both ECG and PK collected) on Day 14 will need to be replaced.

- Additionally, triplicate ECGs will be obtained for safety monitoring at 0 hour (pre-dose) on Day 1 of Cycle 1*, Day 14 of Cycle 2, then on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 will be performed as clinically indicated.

Group 2 (all other patients):

- Triplicate ECGs will be obtained for safety monitoring at 0 hour (pre-dose) on Day 1 of Cycle 1*, Day 14 of Cycles 1 and Cycle 2, then on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 will be performed as clinically indicated.

*NOTE: Triplicate ECGs do not need to be repeated on Day 1 of Cycle 1 if ECG_E was performed within 7 days of the date of randomization.

All triplicate ECG tracings will be sent electronically to a core ECG laboratory for blinded manual interval measurements.

If at any time the mean QTc is prolonged (≥ 501 msec on at least two separate ECGs, ie, CTCAE \geq Grade 3), 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 confirms a QTc of ≥ 501 msec, immediate search for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 501 msec.

- If QTc interval reverts to less than 501 msec, and in the judgment of investigator(s) in consultation with the sponsor the cause is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring under hospital supervision.
- If in that timeframe the QTc intervals remain above 501 msec the study drug will be held until the QTc interval decreases to < 501 msec.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, 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 investigational product causality cannot be ruled out, Investigational product dose adjustment and/or discontinuation should be performed according to [Section 5.3.4: Recommended Dose Modification](#). Additional triplicate ECGs may be performed as clinically indicated.

- b. **Pharmacokinetics (collected right after ECG assessment):** For patients in the ECG Group 1, plasma PK samples for PD-0332991 (including its active metabolites, if appropriate) determination will be obtained at the times indicated for ECGs. One additional plasma PK sample will be collected pre-dose on Day 14 of Cycle 2.

For all other patients (ECG Group 2), plasma PK samples for PD-0332991 (including its active metabolites, if appropriate) determination will be collected prior to dosing (pre-dose) on Day 14 of Cycle 1 and Cycle 2.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

TUMOR ASSESSMENT REQUIREMENTS FLOWCHART

	Screening ^a	Treatment Period ^b	End of Treatment Visit ^c
CT d or MRI of chest, abdomen, and pelvis (CAP)	Required ^e	Required	Required
CT d or MRI of any other site of disease, as clinically indicated	Required ^{e, f}	Required for sites of disease identified at screening	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Radionuclide bone scan (whole body) and correlative bone imaging	Required ^{g, h}	Required for sites of disease identified at screening or if clinically indicated ⁱ	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Photographs of all superficial lesions as applicable ^j	Required	Required for sites of disease identified at screening	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere

- a. Screening scans must occur within 4 weeks (ie, 28 days) prior to randomization unless otherwise specified.
- b. Tumor assessment must be done during the treatment period, every 12 weeks (± 7 days) and bone scans (as applicable) every 24 weeks (± 7 days) from randomization until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anti-cancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow up), whichever occurs first. The schedule of assessments should be fixed according to the calendar, regardless of treatment delays/interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique MUST be used throughout the study for a given lesion/patient.
- c. Patients who have already demonstrated objective disease progression as per RECIST v.1.1 do not need to have scans repeated at the end of treatment visit or during the post-treatment follow-up. For patients who do not have documented objective disease progression at time of study treatment discontinuation, tumor assessment will continue to be performed every 12 weeks (± 7 days) and bone scans (as applicable) every 24 weeks (± 7 days) until radiographically and/or clinically confirmed objective disease progression, initiation of new anti-cancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up).
- d. The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF).
- e. Radiographic assessments obtained per the patient's standard of care prior to randomization into the study do not need to be repeated and are acceptable to use as baseline evaluations, if (1) obtained within 28 days before randomization, (2) they were performed using the method requirements outlined in RECIST v.1.1 (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

- f. Baseline brain scans are only required if signs and symptoms suggest presence of metastatic brain disease. Brain scans performed before the signing of informed consent as routine procedures (but within 6 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. Post-baseline repeat brain scans will only be required only if metastases are suspected.
- g. Bone scans will be carried out at baseline for all patients within 12 weeks prior to randomization in order to detect bony sites of disease. Bone scans performed before the signing of informed consent as routine procedures (but within 12 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.
- h. Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline and on subsequent bone scans **MUST be confirmed** by X-ray, CT scan with bone windows or MRI. The same modality must be used throughout the trial for confirmation for a given lesion/patient. Bone lesions identified at baseline will be followed up according to the same assessment schedule (ie, every 12 weeks \pm 7 days from randomization) as for all other lesions. Areas that have received palliative radiotherapy cannot be used to assess response to study treatment.
- i. If bone lesions were identified at baseline bone scans will be repeated during the active treatment phase every 24 week (\pm 7 days) from the date of randomization and at the time of confirmation of CR. If no bone lesions were identified at baseline, bone scans will only be repeated during the active treatment phase when clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required at the time of confirmation of CR. New Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan with bone windows or MRI.
- j. Clinical assessment of superficial disease must be carried out on the same date as the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the case report form (CRF).

Notes:

- Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator. If progressive disease is confirmed per RECIST v.1.1, patients are expected to discontinue study therapy and begin the follow-up phase of the trial. However, patients may continue treatment as assigned at randomization beyond the time of RECIST-defined PD at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anti-cancer treatment is initiated.

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APPENDICES

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1. INTRODUCTION

Breast cancer (BC) is the most common invasive cancer in women, with more than one million cases and over 411,000 deaths occurring worldwide annually.¹ Although age-adjusted mortality from breast cancer has been decreasing since 1990, the median survival for patients with metastatic disease is still only approximately 18 to 24 months² and the medical need for more active agents in this clinical setting remains very high.

The role of estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormonal receptor positive advanced breast cancer, particularly for those with slowly progressive disease and limited tumor-related symptoms. Letrozole (Femara[®]) is an oral nonsteroidal aromatase inhibitor and it is approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer (ABC).

1.1. Indication

Estrogen receptor-positive (ER(+)), HER2 negative (HER2(-)) Advanced Breast Cancer (ABC)

1.2. Background and Rationale

1.2.1. Role of Letrozole in the Treatment of Estrogen Receptor Positive Breast Cancer

Approximately two-thirds of breast cancers express estrogen receptor (ER)³ and a role for estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormone receptor-positive ABC,² particularly for those with slowly progressive disease and limited tumor-related symptoms.

Conversion of androgens to estrogens via aromatase enzyme action represents the main source of estrogens in postmenopausal women. Letrozole (Femara[®]) is an oral nonsteroidal aromatase inhibitor that is approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive ABC. In a multicenter Phase 3 trial,⁴ 916 patients with hormone receptor-positive or hormone receptor-unknown ABC were randomized to receive either letrozole or tamoxifen until disease progression. Most of the patients (91%) had received no prior treatment for their advanced disease. Letrozole was superior to tamoxifen for time to tumor progression (median, 9.4 vs 6.0 months, $P < 0.0001$), time to treatment failure (median, 9 vs 5.7 months, $P < 0.0001$), overall objective response rate (32% vs 21%, $P = 0.0002$), and overall clinical benefit (50% vs 38%, $P = 0.0004$). Median overall survival (OS) was slightly prolonged for the letrozole arm (34 vs 30 months); however, approximately 50% of the patients in the tamoxifen arm crossed over to letrozole at disease progression.

Letrozole is administered orally on a continuous 2.5 mg daily dosing regimen. Multiple clinical studies have shown that letrozole is well tolerated.

1.2.2. Interaction of Estrogens and Cyclin-Dependent Kinases in Breast Cancer Cells

Studies of ER-positive breast cancer cell lines indicate that estrogens⁵ and antiestrogens⁶ act on sensitive populations of cells in early to mid-G1 phase. G1/S transition is under the control of CDKs activated by specific complex formation with regulatory cyclins. CDK4 and CDK6 are activated by binding to D-type cyclins and act early in G1 phase.^{7, 8, 9, 10} A primary target of CDK action in G1 phase is the retinoblastoma susceptibility gene product (pRb), which mediates G1 arrest through sequestration of transcriptional factors of the E2F-DP family. Phosphorylation of pRb and other members of the pocket protein family (p107 and p130) by active cyclin-CDK complexes leads to release of E2F and DP transcription factors and transcription of requisite genes for S-phase entry.¹⁰

D-type cyclins play an essential role in recognition of extracellular growth stimuli and initiation of G1 transit,^{11, 12} and several lines of evidence have linked estrogen regulation of cellular proliferation to cyclin D1 expression. Estrogen-induced proliferation of normal uterine and breast epithelium *in vivo* is associated with increased expression of cyclin D1 mRNA and protein.^{13, 14, 15, 16} Expression of cyclin D1 in breast tumor isolates correlates with ER-positive status.^{17, 18, 19} MCF-7 breast cancer cells treated with estrogen exhibit increased expression of cyclin D1 mRNA and protein, formation of active cyclin D1-CDK4 complexes, and phosphorylation of pRb leading to G1 /S transition.^{20, 21, 22, 23} Estrogen-induced S-phase entry in these cells is inhibited by microinjection of antibodies to cyclin D1.²⁴ Antiestrogen-induced growth arrest of ER-positive breast cancer cells is associated with decreased cyclin D1 expression.²⁵ Collectively, these studies are consistent with a model of estrogen action in which receptor activation induces increased cyclin D1 expression, CDK4 activation, and cell cycle progression. An upstream role for cyclin D1 has been suggested by recent reports describing direct physical interactions between cyclin D1 and the ER, leading to recruitment of steroid receptor coactivators and activation of ER-dependent transcription. This occurs in the absence of hormone and is independent of D-type cyclin association with CDK4.^{26, 27, 28, 29}

Constraint upon CDK activity and G1 progression is provided by the universal CDK inhibitors of the Cip-Kip family, including gp21Cip1 and p27Kip1, and the specific CDK4 and CDK6 inhibitors of the INK4 family, typified by p16^{INK4a}.^{12, 30, 31, 32, 33} The CDKN2A gene product inhibits formation of active D-type cyclin-CDK complexes through specific binding interactions with CDK4 or CDK6 that prevent D-type cyclin-CDK association.^{34, 35, 36} Over expression of p16^{INK4a} in cells with functional pRb results in inhibition of both CDK4-and CDK6-associated kinase activity and pRb phosphorylation, with subsequent cell cycle arrest.^{34, 35} In addition, inhibition of D-type cyclin-CDK4 complex formation by p16^{INK4a} prevents sequestration of p21^{Cip1} and p27^{Kip1} by these complexes in early G1, leading to suppression of cyclin E-CDK2 activity.^{37, 38, 39}

Overexpression of p16^{INK4a} through adenoviral transduction of CDKN2A into MCF-7 cells leads to G1 arrest associated with inhibited CDK activity.^{40, 41} Cell cycle progression induced by estradiol requires action of the steroid through mid-G1, well beyond the point of cyclin D1-CDK4 activation.²¹ Functional association of cyclin D1-CDK4 is required for estrogen-induced CDK2 activation and G1/S transition and estrogen regulates expression of p21^{Cip1}, p27^{Kip1}, and Cdc25A independent of D-type cyclin-CDK4 function.⁴²

1.2.3. Deregulation of Cell Cycle Related Genes and Proteins in Breast Cancer

Cell cycle related genes and proteins are frequently deregulated in breast cancer. Approximately 15%–20% of human breast cancers exhibit amplification of the cyclin D1 (CCND1) gene,^{43, 44, 45} while the majority of human mammary carcinomas over express cyclin D1 protein.^{46, 47, 48} Over expression of cyclin D1 is seen early in breast cancer, and it is maintained at all stages of breast cancer progression, including metastatic lesions.^{46, 49} Amplification of the CDK4 gene, located at 12q13-q14, has been shown as an alternative genetic alteration to CDKN2A inactivation in various human tumor including breast cancer.^{50, 51} There is a mounting body of evidence linking a specific CCND1 polymorphism (G/A870) to increased risk of cancer and outcome in a variety of tumor types including breast cancer. This polymorphism results in a splice variant, altered protein structure and enhanced oncogenic activity in experimental models.⁵² The continued presence of CDK4-associated kinase activity is actually required to maintain breast tumorigenesis.⁵³ Direct analyses of primary tumors have revealed loss of pRb expression in 20–35% of tumors, and loss of heterozygosity or other alterations of the Rb locus in 7–37% of tumors.^{54, 55, 56, 57} In preclinical models, Rb depletion appears to be associated with resistance to antiestrogen therapy.⁵⁸ Finally, virtually all ER-positive cell lines harbor loss of p16^{INK4a}^{59, 60} expression, and low expression of CDK inhibitors p21 and p27 and high expression level of cyclin E and D1 have all been associated with resistance to anti-estrogen therapy.

1.2.4. ER and HER2 Status in Breast Cancer

The ER and HER2 status of breast metastatic disease are usually assumed to be the same as that of the primary tumor. However, mounting evidences from both prospective and retrospective studies have shown a discordant rate of approximately 25% in either ER or HER2 status between primary breast tumor and its metastatic lesions.^{61, 62} The change can be from ER- positive primary tumor to ER-negative metastatic disease or vice versa. The analytical variables of immunohistochemistry (IHC) testing such as antigen retrieval and subjectivity in observer analysis also contribute to the observed discordance.⁶³ Another dilemma in ER testing accuracy has been primary institutional site testing versus high volume central laboratory testing. It has been stated in the recently published American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for ER testing that the concordance rate between local and central laboratory testing for ER is about 80 to 90%.⁶⁴ This variation may be due to the lack of rigorous assay optimization and/or reproducibility of IHC testing procedures at some of local testing laboratories including methods of antigen retrieval and subjectivity in observer analysis. This highlights the importance of confirmative testing of ER status using Food and Drug Administration (FDA)-cleared and/or approved kits and platform at a central CLIA/CAP certified laboratory to minimize, if not eliminate, these differences/variables for patients participating in clinical trials.

1.2.5. Overview of PD-0332991

PD-0332991 (Molecular Weight: 573.67) is an orally active potent and highly selective reversible inhibitor of CDK4 and CDK6. The compound prevents cellular deoxyribonucleic acid (DNA) synthesis by prohibiting progression of the cell cycle from G1 into the S phase.

1.2.5.1. Preclinical Data

Treatment of cultured tumor cells with PD-0332991 causes growth arrest that is accompanied by the inhibition of specific pRb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of pRb. The IC₅₀ values for reduction of pRb phosphorylation at serine -780 and -795 in MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 μM, respectively. The IC₅₀ values for reduction of pRb phosphorylation are similar to the IC₅₀ values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

PD-0332991 was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to PD-0332991 (IC₅₀ <150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. Sensitive cell lines in this panel represent mostly the luminal ER+ subtype.⁶⁵ The combination of PD-0332991 and aromatase inhibitors has not been tested in preclinical models. However, the combination of PD-0332991 with tamoxifen has recently been tested in vitro in ER+ human breast cancer cell lines indicating a synergistic interaction⁶⁵ and provides a biologic rationale for evaluating the combination of PD-0332991 with anti-hormonal therapy in the clinic.

1.2.5.2. Human Pharmacokinetic (PK) Data

To date, pharmacokinetic data have been collected in 4 clinical studies in cancer patients (A5481001, A5481002, A5481003 and A5481004). Pharmacokinetic parameters are available from all 74 patients enrolled in Study A5481001 following a single dose (Day 1 of Cycle 1), and from 51 patients following multiple-dose administration (Day 8 of Cycle 1) at daily doses ranging from 25 to 225 mg of PD-0332991. In addition, PK parameters are also available for nine patients on Day 14 of Cycle 1 (from patients on Schedule 2/1, ie, 2 weeks on treatment followed by 1 week off treatment) and 4 patients on Day 21 of Cycle 1 (from patients on Schedule 3/1, ie, 3 weeks on treatment followed by 1 week off treatment). The exposure (AUC₍₀₋₁₀₎ and C_{max}) increased in a dose proportional manner over the dose range of 25 to 225 mg once daily (QD) following PD-0332991 administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level. Following repeated daily dosing to Day 14 and Day 21 (assumed to be steady state), PD-0332991 was absorbed with a median T_{max} of ~4 hours. The mean PD-0332991 V_Z/F was 3103 L, which is significantly greater than total body water (42 L), indicating that PD-0332991 extensively penetrates into peripheral tissues. PD-0332991 was eliminated slowly; the mean t_{1/2} was 26.5 hours (ranged 15.8 to 36.2 hours) and the mean CL/F was 86.1 L/hour. PD-0332991 accumulated following repeated dosing with a median R_{ac} of 2.4, which is consistent with a half life of ~27 hours.

Preliminary results from the recently performed food effect study, *A5481021, a Phase 1, open-label 4 sequence 4 period crossover study of palbociclib (PD-0332991) in healthy volunteers to estimate the effect of food on the bioavailability of palbociclib*, suggest that the administration of palbociclib with food results in more consistent drug absorption and exposure than administration of palbociclib in a fasted state. As a result of these findings, patients should be instructed to take palbociclib with food.

Preliminary results from the recently performed antacid effect study, *A5481018, a Phase 1, open-label fixed-sequence 2-period crossover study of palbociclib in healthy subjects to investigate the potential effect of antacid treatment on the pharmacokinetics of a single oral dose administered under fasted conditions*, suggest that the administration of proton-pump inhibitors concomitantly with palbociclib treatment leads to a significant decrease in palbociclib exposure. Since proton-pump inhibitors affect the pH of the upper GI tract for an extended period the concomitant use of proton-pump inhibitors with PD-0332991 should be avoided.

Study A5481038, a Phase 1 study was designed to investigate the effect of famotidine (an histamine H₂-receptor antagonist) given 10 hours before and 2 hours after palbociclib; rabeprazole sodium (a proton-pump inhibitor) given daily for 6 days before and 4 hours prior to palbociclib; mi-acid maximum strength liquid given 2 hours before palbociclib; mi-acid maximum strength liquid given 2 hours after palbociclib on the relative bioavailability of a single oral 125 mg of palbociclib commercial free base hard capsule formulation dose given under fed conditions in healthy volunteers. The results from this study showed that famotidine given 10 hours before and 2 hours after palbociclib or mi-acid maximum strength liquid (local antacid) given 2 hours before or 2 hours after palbociclib did not impact the exposure of palbociclib. Additionally, the results showed that coadministration of rabeprazole and palbociclib under fed conditions resulted in a decrease in palbociclib exposure less dramatic than the change in exposure observed in study A5481018 where palbociclib was administered under fasted conditions. Palbociclib change in geometric mean C_{max} in combination with daily administration of rabeprazole decreased by 41% under fed conditions compared to the 80% decrease under fasted conditions. The change in AUC_{inf} of palbociclib when coadministered with rabeprazole under the fed conditions was approximately 13% compared to palbociclib given alone. Based upon this data, under fed conditions, the use of H₂-receptor antagonists or local antacids is now permitted as defined in [Section 5.5.3](#). As proton-pump inhibitors affect palbociclib C_{max} and to a lesser extent AUC_{inf} their concomitant use will remain prohibited during the active treatment phase as outlined in [Section 5.5.1](#). Should the use of proton-pump inhibitor be required for a given patient, please contact the sponsor for an assessment of the best treatment choice.

Pharmacokinetic data from Study A5481002 indicate that PD-0332991 exposure at steady state in mantle cell lymphoma patients, is similar to that observed in solid tumors (Protocol A5481001).

Pharmacokinetic analysis of preliminary data from the Phase 1 portion of Study A5481003 (breast cancer, combination with letrozole) was conducted to evaluate the potential for drug-drug interaction between PD-0332991 and letrozole. The results indicate lack of a potential for drug-drug interaction between PD-0332991 and letrozole when administered in combination.

PD-0332991 is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, PD-0332991 is primarily metabolized by CYP3A4 enzymes. An exploratory evaluation of the circulating metabolites for PD-0332991 was conducted in plasma samples obtained from patients treated with PD-0332991 200 mg QD (Schedule 2/1) in Study A5481001. Preliminary assessment of the pooled plasma samples on Day 14 of Cycle 1 indicated that the glucuronide conjugate of PD-0332991 and the lactam of PD-0332991 (PF-05089326) were the main metabolites present in plasma. Other metabolites observed were the glucuronide conjugates of hydroxylated PD-0332991 and the glucuronide conjugate of reduced PD-0332991. PF-05089326 was also observed in the circulation of rats following repeated daily oral administration of PD-0332991 at the dose levels of 50 and 100 mg/kg/day. Plasma protein binding of PD-0332991 and PF-05089326 is ~85% and 95%, respectively.

1.2.5.3. QTc Evaluation Data

In vitro (hERG) and in vivo (dog telemetry) studies revealed a potential for QT prolongation at unbound concentrations ≥ 14 -fold the unbound steady-state C_{\max} associated with the clinical dose of 125 mg QD (refer to the PD-0332991 investigator's brochure for additional details).

A preliminary pharmacokinetic/pharmacodynamic analysis has been conducted to explore the QT/QTc and plasma PD-032991 concentration relationship for Study A5481001 (FIH study) by using graphical methods and mixed effects linear modeling (NONMEM). Data from 73 patients were used for the analysis, and an analysis of the QTcF and QTcB data demonstrated that QTcF was the more appropriate correction method based on plots of the QTc versus RR interval. No patient had a maximum on treatment QTcF value of ≥ 500 msec. The QTcF changes from the baseline at the mean C_{\max} calculated for 200 mg dose were simulated for 10000 patients. The mean and upper 95% confidence interval of QTcF change from the baseline were 5.8 and 9.4 msec, respectively.

In order to achieve more extensive evaluation of the effect of PD-0332991 on QTc prolongation, time-matched electrocardiogram (ECG) and PK data will be collected in a subset of at least 60 patients participating to Study A5481008 (see [Schedule of Activities](#) table and [Section 7.2.2](#) for further details).

1.2.5.4. Preclinical Ocular Data

Preliminary results from an ongoing 27-week repeat-dose oral toxicity study with PD-0332991 in Sprague-Dawley rats identified a potential nonclinical safety finding related to the eye. Palbociclib was administered by oral gavage at doses of 0, 10, 30, and 100 mg/kg/day in males and 0, 50, 100, and 300 mg/kg/day in females (20/sex/group;

15/sex/group in main and 5/sex/group in recovery) on an intermittent dosing schedule (7 cycles of treatment where each cycle consisted of 3 weeks of continuous daily dosing followed by a 1-week non-dosing period) for 27 weeks. Animals were evaluated by indirect ophthalmoscopy and by slit lamp biomicroscopy predose and prior to termination (within 7 days prior to scheduled necropsy). Indirect ophthalmoscopy results revealed a degraded view of the fundus and the presence of cataracts in males treated at high dose (100 mg/kg/day) that had normal fundus examinations prior to the start of the study. Cataracts (anterior cortical, incomplete, and complete) were identified by slit lamp biomicroscopy in male rats at ≥ 30 mg/kg/day with dose-related severity (Table 1), but not in females at any dose tested (up to 300 mg/kg/day).

Lens degeneration was observed microscopically with dose-related incidence and with minimal to moderate severity in males at ≥ 30 mg/kg/day and minimal severity in males at 10 mg/kg/day and females at ≤ 100 mg/kg/day (not identified in females at 300 mg/kg/day). Lens degeneration was identified in all animals that were noted with cataracts by slit lamp ophthalmoscopy.

The available data suggests that the cataracts and/or lens degeneration observed at the lowest doses in both male and female rats are palbociclib-related. Exposures in this non clinical study are comparable to clinical exposures at the recommended human dose of 125 mg QD (unbound AUC 301 ng•h/mL).

The mechanism for cataract formation in palbociclib-treated rats is unknown; however, emergent data from the 27-week rat toxicity study suggested its pathogenesis in rats may be related to altered glucose metabolism. Ten of 11 male rats with lens degeneration were shown to have glycosuria (+2 or +3) and/or increased serum glucose (compared to the upper range of control values). One of 3 female rats with lens degeneration also had glycosuria and hyperglycemia. In addition to the correlation observed between altered glucose metabolism and lens degeneration, a correlation between altered glucose metabolism and pancreatic islet cell vacuolation was identified in all (10 of 10) male animals with the histological change. In females, the one female with lens degeneration that correlated with glycosuria and hyperglycemia also had pancreatic islet cell vacuolation. No altered glucose levels, cataracts/lens degeneration, or pancreatic islet cell vacuolation have been observed in the 39-week dog toxicity study.

To date, approximately 1200 patients have enrolled in palbociclib trials. A review of the Pfizer safety database for cases received through 14 January 2014 identified no serious cases from clinical studies or other solicited sources including palbociclib or blinded therapy that included adverse events which code to the MedDRA (Version 16.1) High Level Group Term "Anterior eye structural change, deposit and degeneration". In addition, no cases coding to the afore mentioned MedDRA term were reported to the safety database from any other sources during this period for patients who received palbociclib. Cataract has been reported as an adverse event in 2 patients (1 Grade 2 and 1 Grade 3) out of approximately 400 patients who have been treated with palbociclib in Pfizer-sponsored studies. Neither event was considered serious nor related to palbociclib and both patients had other identifiable risk factors for cataracts, such as age and long term corticosteroid use. Both patients continued on treatment for 16-18 months beyond the diagnosis of cataract.

It is interesting to note that literature reports suggest that the incidence of cataract in women aged 35 and older with risk of breast cancer is approximately 2.3%.⁶⁷ Cataract is also a known finding in patients treated with tamoxifen or letrozole.^{66, 67}

Given the observed nonclinical findings in rats, palbociclib clinical studies were also carefully reviewed for adverse events relevant to a new diagnosis of diabetes or hyperglycemia. Baseline and on-study glucose data were collected as part of the Palbociclib A5481001 first-in-human Phase 1 trial (N= 74). In this trial, 2 treatment schedules (3 weeks on/1 week off [n= 39]; and 2 weeks on /1 week off [n= 33]) were evaluated at escalating dosing levels (25-225mg) of single-agent palbociclib. In the 3/1 and 2/1 schedules, 16 (41.0%) and 12 (36.4%) subjects experienced a worsening of serum glucose to Grade 1 from their pre study baseline, respectively; 6 (15.4%) and 2 (6.1%) worsening to Grade 2 from their baseline, respectively; and 1 (2.6%) and 2 (6.1%) worsening to Grade 3 from their baseline, respectively. No subjects experienced a worsening of serum glucose to Grade 4 from their baseline on this study. Of the 4 cases of Grade 3 elevated serum glucose measurements observed on-study (independent of worsening from baseline), 3 occurred in patients known to be diabetic at time of study entry, and 1 case was observed in a patient being treated with short-term steroids for a gastrointestinal toxicity. Additionally, there were no report of newly diagnosed cases of diabetes mellitus on study. There was a median number of 2 treatment cycles received by patients in both treatment schedules and although no statement can be made about potential chronic effects of palbociclib in humans, the available data do not suggest any apparent effect of duration of exposure or dose on glucose levels. Additionally, the incidence of hyperglycemia seen in Study A5481001 may be explained by the characteristics of this advanced cancer patient population.

Glucose laboratory tests were not collected in the PALOMA-1 (A5481003) randomized Phase 1/2 trial of Palbociclib in combination with letrozole in first line metastatic breast cancer patients (n= 172 received study treatment); however, clinical adverse event reports of elevated glucose levels or diabetes mellitus terms were evaluated. On the palbociclib + letrozole arm, in patients known to be non-diabetic (n = 85) there was 1 report of Grade 2 diabetes mellitus in a patient who started to receive an anti-diabetic medication while on study. In patients known to be diabetic (n = 10), there was 1 report of Grade 2 hyperglycaemia. On the letrozole alone arm, in patients known to be non-diabetic (n =71) there was 1 report of Grade 2 diabetes mellitus in a patient who also started to receive an anti-diabetic medication while on study, and 1 report of Grade 1 hyperglycaemia in another patient who did not initiate any anti-diabetic medication. In patients known to be diabetic (n = 6) there were no reports of hyperglycaemia. In summary, there was no apparent imbalance in the rate of hyperglycemia/diabetes mellitus adverse events in PALOMA-1.

Based on the review of the available clinical data, there does not appear to be a clinical association of hyperglycemia and diabetes mellitus with palbociclib at this time. However, the current clinical dataset is limited and therefore, in order to prospectively characterize whether or not there is an impact of palbociclib on glucose metabolism, monitoring of appropriate laboratory measurements is being implemented in ongoing and future palbociclib studies.

1.2.5.5. PD-0332991 Dose Rationale

PD-0332991 has been tested in a Phase 1 dose escalation Study (A5481001) in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment/1 week off treatment) and Schedule 2/1 (2 weeks on treatment/1 week off treatment).

All DLTs observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and non-cumulative. The most common non-hematological adverse events included fatigue, anemia, diarrhea, constipation, vomiting and dyspnea, all with mild to moderate severity. A greater proportion of patients on the 2/1 schedule had treatment-related TEAEs during and after Cycle 1 than patients on the 3/1 schedule although the proportion of patients with treatment-related neutropenia was similar with respect to the 2 dosing schedules, both during and after Cycle 1. One partial response was reported in a patient with testicular cancer. A total of 13/37 patients treated with Schedule 3/1 evaluable for efficacy experienced stable disease (SD), including 6 patients with SD lasting 40 weeks or longer. One of these patients was a woman with ER+ breast cancer who had previously received 7 lines of treatment for her disease. This patient remained on treatment for 80 weeks (7 cycles at 50 mg/d and 13 cycles at 75 mg/d) and eventually discontinued treatment due to disease progression. Based on the relatively improved safety profile of Schedule 3/1, and the efficacy results from this study, the Schedule 3/1 has been selected for further clinical development and the RP2D for this schedule was determined to be 125 mg/d. This schedule and associated RP2D was further explored in combination with letrozole in the Phase I/II study in patients with ABC described below.

1.2.5.6. Phase I/II Data in Combination with Letrozole in Advanced Breast Cancer

Based on the preclinical evidence that PD-0332991 is highly active in ER(+) cell lines and the encouraging safety and PK profiles observed in the initial clinical studies, a randomized, multicenter active-controlled Phase 1/2 Study (A5481003) was designed to assess the efficacy, safety and pharmacokinetics of letrozole 2.5 mg QD (continuously) in combination with PD-0332991 125 mg QD (schedule 3/1) versus single agent letrozole 2.5 mg QD (continuously) for the first-line treatment of ER(+), HER2 (-) ABC in postmenopausal women. Letrozole was selected as the active control based on its worldwide approval and use as standard of care for the first-line hormonal treatment of postmenopausal women with ER(+) ABC.

Study A5481003 was comprised of a limited Phase 1 portion, aimed at confirming the safety and tolerability of the combination and excluding a PK interaction with the combination, and a randomized Phase 2 portion aimed at evaluating the efficacy and safety of letrozole in combination with PD-0332991 when compared to letrozole alone in the first-line treatment of postmenopausal patients with ER(+), HER2(-) ABC. The Phase 2 portion consisted of 2 parts. In Part 1, patient selection was based only on ER/HER2 status. In Part 2, patients were prospectively selected also taking into account tumor CCND1 amplification and/or p16 loss. As of 18 May 2012, 177 patients have been enrolled in this study and enrollment is closed. Twelve (12) were enrolled in the Phase 1 portion and 165 (66 and 99 in Part 1 and 2, respectively) were enrolled in the Phase 2 portion.

Results from the Phase 1 portion,⁶⁸ indicated no PK interaction between PD-0332991 and letrozole with mean AUC(0-24) of 2002 and 2043 ng•hr/mL (n=11) for PD-0332991 in the absence and presence of letrozole, respectively, and 1990 and 1730 ng•hr/mL (n=10) for letrozole in the absence and presence of PD-0332991, respectively. The RP2D was determined to be 125 mg QD on Schedule 3/1 (3 weeks continuous treatment followed by 1 week off treatment) in combination with letrozole 2.5 mg QD continuously. Partial responses were reported for 3 (33%) out of 9 patients with measurable disease (3 had bone-only disease). Another 5 patients (42%) had stable disease for ≥6 months and the clinical benefit rate (PR + SD ≥6 months) was 67%. Eight (8) patients discontinued from the study due to disease progression, including 2 patients with clinical progression, and 4 patients are still ongoing.

Preliminary results from Part 1 of the Phase 2 portion were presented at the 2012 IMPAKT Breast Cancer Conference⁶⁹ and included a total of 66 postmenopausal women with ER(+) / HER2(-) locally recurrent or metastatic breast cancer randomized to either receive PD-0332991 in combination with letrozole (n=34 patients) or letrozole monotherapy (n=32 patients).

The combination therapy was generally well tolerated when compared to letrozole alone with AEs similar to those seen with PD-0332991 and letrozole when administered alone. Uncomplicated neutropenia, leucopenia and fatigue were the most frequent adverse events with neutropenia (54%), leucopenia (21%) being the most commonly reported Grade 2 events in patients treated with the combination therapy. Grade 4 events included neutropenia and fatigue, each reported in 6% of patients treated with PD-0332991 + letrozole. No Grade 4 events were reported in the letrozole alone arm. Treatment-related Grade 1/2 AEs reported more frequently in patients in the PD-0332991 + letrozole arm compared with the letrozole alone arm included: leukopenia, anemia, fatigue, alopecia, arthralgia, nausea, neutropenia, and thrombocytopenia. Hot flush was the most common Grade 1/2 treatment-related AE reported in patients enrolled in the letrozole alone arm.

Overall, 3 (9%) patients in the PD-0332991 + letrozole arm and 1 (3%) patient in the letrozole arm discontinued the Part 1 Phase 2 of Study A5481003 due to AEs including: 1 patient with Grade 4 fatigue (not related to PD-0332991) and 2 patients with Grade 3 neutropenia in the PD-0332991 + letrozole arm and 1 patient with Grade 2 nausea in the letrozole alone arm. The median duration of treatment was 13.7 months in the PD-0332991 + letrozole arm vs 5.4 months in the letrozole alone arm, with PD-0332991 dosing interruptions and dose reductions due to AEs reported in 61% and 39% of patients enrolled in the PD-0332991 + letrozole arm, respectively. The median duration of dosing interruptions was 4.5 days and the median time to first dosing interruption was 55.5 days. Despite the dosing interruptions and/or reductions, the median dose intensity for PD-0332991 was 87% across all cycles.

Efficacy analyses were performed on the basis of radiologic assessment of disease status by investigators to determine preliminary antitumor activity according to RECIST v.1.0. After a median follow-up of 16.5 months, median PFS was prolonged in patients who received

combination therapy compared to letrozole alone (18.2 months vs 5.7 months). Objective response and clinical benefit rates (52% vs 32% and 76% vs 47%, respectively) were also superior with the combination therapy. No complete responses were observed. Data from the Part 2 are not yet mature.

These results indicate that the combination of PD-0332991 with letrozole is well tolerated with AEs similar to those seen with either PD-0332991 or letrozole when administered alone. Additionally, the combination demonstrated antitumor activity which was consistent with the sensitivity of ER(+) breast cancer observed in the preclinical models. Results from Part 2 are not yet available.

1.2.6. Study Rationale

In the first-line treatment setting, letrozole is among the preferred anti-hormonal therapies for postmenopausal women with ER(+)/HER2(-) ABC.⁷⁰ It is approved and commercially available globally with a well known and manageable safety profile. However, median progression-free survival in this patient population remains less than 1 year and median overall survival is approximately 3 years.⁴ Furthermore, aromatase inhibitor failure has been linked to increased proliferative index and cell cycle dysregulation, providing a strong rationale for combining letrozole with PD-0332991. Preliminary data from Phase 1/2 Study A5481003 suggest that the combination of PD-0332991 inhibition of CDK 4/6 (blocking DNA synthesis by prohibiting progression of the cell cycle from G1 to S phase) with the antiproliferative effects of letrozole provides greater antitumor activity and prolongs PFS (ie, median 18.2 months vs 5.7 months) when compared to single agent letrozole. Additionally, the study shows that the combination is generally well tolerated with uncomplicated neutropenia as the most frequent adverse event.⁶⁹

The current Phase 3 study provides the opportunity to confirm the clinical benefit of the combination of PD-0332991 with letrozole observed in Study A5481003. The study is designed to demonstrate that PD-0332991 in combination with letrozole provides superior clinical benefit compared to letrozole in combination with placebo in postmenopausal women with ER(+)/HER2(-) locoregionally recurrent or metastatic breast cancer who have not received any prior systemic anti-cancer therapies for their advanced disease.

Complete information for PD-0332991 may be found in the Single Reference Safety Document for the compound, which for this study is the Investigator's Brochure. The Single Reference Safety Document for the active comparator agent, letrozole, is the United Kingdom (UK) Summary of Product Characteristics (SPC) for Femara.⁶⁶

1.2.7. Amendment Rationale

1.2.7.1. Rationale for Changes in Amendment 1, 01 October 2013

Protocol was amended to address a specific request from the French Regulatory Agency to emphasize the importance of obtaining tumor tissue from a recurrence/metastatic disease at the time of study entry. The protocol language was revised accordingly and implemented for France only.

1.2.7.2. Rationale for Changes in Amendment 2, 03 January 2014

Preliminary results from two clinical pharmacology studies A5481018 and A5481021 suggested that palbociclib exposure may be decreased when administered in a minimally fasted state or concomitantly with proton-pump inhibitors. Therefore the protocol was amended to revise the study drug administration instructions from administration in a minimally fasted state to administration with food and also to prohibit the concomitant use of proton-pump inhibitors.

Additional changes included clarification to some protocol eligibility criteria to address the most frequently asked eligibility-related questions and minimize potential patient enrollment errors.

1.2.7.3. Rationale for Changes in Amendment 3, 21 March 2014

Taking into account the preliminary results from studies A5481018 and A5481021, it was assumed that drug exposures before and after implementation of Amendment 2 might be different in patients who took palbociclib in a minimally fasted state (ie, fast from 1 hour before to 2 hours after dosing) and/or concomitantly with proton-pump inhibitors compared to those patients who did not. This difference could potentially reduce the statistical power to detect the true treatment effect of palbociclib in the intent to treat (ITT) population under the current study design. As a result, the protocol is being amended prior to the interim analysis to increase the sample size from 450 patients to 650 patients to preserve the desired statistical power.

Additionally, based on the limited pre-clinical and clinical data currently available, it is not known whether true clinical risk exists for developing palbociclib-associated cataracts. The protocol is therefore being amended to implement prospective ophthalmic assessments in all newly enrolled, lens grading patients at baseline and while on study treatment. The results of the ophthalmic assessments will provide a better understanding of the risk of ocular adverse events and will provide information to determine whether further actions are warranted.

1.2.7.4. Rationale for Changes in Amendment 4, 18 September 2014

Given the observed nonclinical findings in rats and taking into account the limited laboratory glucose data in the current clinical dataset, the protocol was amended in order to prospectively characterize whether or not palbociclib affects glucose metabolism, through monitoring of appropriate laboratory measurements.

Additionally, the protocol was amended to reflect the Sponsor's decision to no longer require safety review by the IOBU-SDMC for studies already monitored by an E-DMC.

Language related to cycle delay was also further defined to clearly state that any new cycle may only start if blinded study treatment can be resumed.

Lastly, further clarification, was also added in the Concomitant Medications [Section 5.5](#): editorial changes were made to differentiate between strong and moderate CYP3A inducers/inhibitors, restriction on CYP3A substrate was removed based on updated information indicating that palbociclib is a weak time-dependent inhibitor of CYP3A, and local antacids and H₂-receptor antagonists were moved under the "Permitted Medications" [Section 5.5.3](#) to reflect results from study A5481038 showing that H₂-receptor antagonists and local antacids given as defined per protocol do not impact the exposure of palbociclib.

1.2.7.5. Rationale for Changes in Amendment 5, 02 December 2014

In the current study design, an interim analysis will be performed after approximately 266 PFS events occur (about 65% of total PFS events needed for final analysis) using O'Brien-Fleming efficacy boundary (Lan-DeMets procedure). Under these conditions, the study could be stopped for efficacy if $z \geq 2.5469$ which would equate to a hazard ratio (HR) ≤ 0.6979 , or about 4 months improvement in median PFS if the median PFS of the control arm is exactly 9 months as the study design assumed. In this instance, the interim efficacy boundary, while reaching statistical significance, may not represent a clinically meaningful improvement.

The interim analysis is being revised in this protocol amendment to ensure that the study would only be stopped at the interim analysis if the primary analysis (PFS) results are statistically significant and clinically meaningful.

Language related to the analysis of the primary endpoint was updated to further define the planned analysis.

Additionally, the protocol is being amended to allow the concomitant use of strong/moderate CYP3A inducers/inhibitors and proton-pump inhibitors for patients who permanently discontinue blinded therapy but continue on study with letrozole monotherapy only.

Finally, editorial changes were made to the drug destruction supply instruction to reflect current trial practices.

1.2.7.6. Rationale for Changes in Amendment 6, 07 April 2015

In order to assess the breast cancer specific quality of life of patients beyond progression in the follow-up period, patient reported outcomes using the FACT-B questionnaire will continue to be collected every 6 months.

Additionally, editorial changes to the adverse event reporting section, the quality control and quality assurance section as well as the publication of study results section were done to reflect the current sponsor's protocol template.

1.2.7.7. Rationale for Changes in Amendment 7, 15 October 2015

In order to better understand the potential influence of palbociclib on response to subsequent anti-cancer treatments, the study is being amended to collect the date of disease progression while on subsequent anti-cancer therapy in addition to the follow-up anti-cancer therapy details already collected (ie, regimen number, name of therapy, and start/stop dates).

The protocol is also being amended to incorporate editorial changes plus remind participating investigators of the requirement for patients to complete their 7-day off treatment period in any given cycle prior to resuming blinded therapy.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective(s)

- To demonstrate that the combination of PD-0332991 with letrozole is superior to placebo plus letrozole in prolonging PFS in postmenopausal women with ER(+)/HER2 (-) advanced breast cancer who have not received any prior systemic anti-cancer therapies for their advanced/metastatic disease.

Secondary Objective(s)

- To compare measures of tumor control duration and overall survival between the treatment arms;
- To compare safety and tolerability between the treatment arms;
- To compare health related quality of life between the treatment arms;
- To characterize the effects of PD-0332991 at therapeutic doses in combination with letrozole on QTc interval in this patient population;
- To determine trough PD-0332991 plasma concentration in this patient population and explore correlations between exposure and response and/or safety findings;
- To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle (eg, CCND1 amplification, CDKN2A deletion), drug targets (eg, CDK 4/6), and tumor sensitivity and/or resistance (eg, Ki67, pRb) in tumor tissues.

2.2. Endpoints

Primary Endpoint(s)

- Progression-Free Survival (PFS).

Secondary Endpoint(s)

- Overall Survival (OS);
- 1-year, 2-year, and 3-year survival probabilities;
- Objective Response (OR: Complete Response or Partial Response);
- Duration of Response (DR);
- Disease Control (DC: CR+PR+Stable disease \geq 24 weeks);
- Corrected QT interval (QTc);
- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1, CDKN2A), proteins (eg, Ki67, pRb), and RNA expression (eg, cdk4, cdk6);
- Trough plasma concentration of PD-0332991;
- EuroQol (EQ-5D) Score (see [Appendix 5](#));
- Functional Assessment of Cancer Therapy - Breast (FACT-B) (See [Appendix 6](#));
- Type, incidence, severity (as graded by NCI CTCAE v4.0), seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.

3. STUDY DESIGN

This is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical trial comparing the efficacy and safety of PD-0332991 in combination with letrozole versus placebo in combination with letrozole in postmenopausal women with ER(+)/HER2 (-) advanced breast cancer. Eligible patients will have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease and will be candidates to receive letrozole as first-line treatment for their advanced disease. In order to avoid inclusion of patients who are refractory or resistant to non-steroidal aromatase inhibitors, patients who received anastrozole or letrozole as a component of their (neo)adjuvant regimen may only enter the study if their disease did not progress while on or within 12 months from completion of their anastrozole/letrozole-containing (neo)adjuvant therapy. Patients will not have received any prior systemic anti-cancer therapies for their advanced disease and will not be candidates for curative therapies. Patients must have measurable disease as per RECIST v.1.1 or bone disease as their only site of disease. Tumor tissue availability is required for patient participation.

At least 650 eligible patients will be randomized 2:1 to receive either PD-0332991 plus letrozole (Arm A: at least 433 patients) or placebo plus letrozole (Arm B: at least 217 patients). Patients will be stratified by site of disease (visceral* vs non-visceral**), by disease-free interval since completion of prior (neo)adjuvant therapy (de novo metastatic; ≤12 months; >12 months), and by the nature of prior (neo)adjuvant anti-cancer treatment received (prior hormonal therapy; no prior hormonal therapy).

*"Visceral" refers to any lung (including pleura) and/or liver involvement.

**"Non-visceral" refers to absence of lung (including pleura) and/or liver involvement.

Patients randomized to Arm A (experimental arm) will receive:

- PD-0332991, 125 mg, orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

in combination with

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients randomized to Arm B (control arm) will receive:

- Placebo orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

in combination with

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients will continue to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. However, patients may continue treatment as assigned at randomization beyond the time of RECIST-defined PD at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anti-cancer treatment is initiated. In this case, the patient would continue with routine safety relevant assessments as per the [Schedule of Activities](#) for the active treatment period.

The importance of timely and complete disease assessments in this study cannot be overstated. Disease assessments will be performed every 12 weeks (± 7 days) from the date of randomization. Patients with bone lesions identified at baseline will also have repeat bone scans performed every 24 weeks (± 7 days) from the date of randomization. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anti-cancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

A series of incomplete disease assessments will result in censoring of the primary endpoint of PFS back to the time of the last full assessment that did not show progression.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie for photographed or palpable lesions) documented PD as per RECIST v.1.1 will continue to have tumor assessments performed during the follow-up visits every 12 weeks (± 7 days) and bone scans (if applicable) every 24 weeks (± 7 days) until RECIST-defined disease progression, initiation of new anti-cancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

Efficacy analyses will be performed using the local radiologist's/investigator's tumor assessments as primary data source. However, a blinded independent third-party core imaging laboratory will complete a retrospective review of radiographic images and clinical information collected on-study to verify the protocol-defined endpoints of disease response and progression as assessed by the investigator.

Patients discontinuing the active treatment phase will enter a follow-up period during which FACT-B questionnaire, survival and new anti-cancer therapy information (including regimen number, name of therapy, start/stop dates, and dates of disease progression on subsequent anti-cancer therapies) will be collected every 6 months from the last dose of investigational product. The follow-up period will conclude at the time of the final OS analysis. Crossover will not be allowed in the trial.

Patients will undergo study-related safety, efficacy, and PK assessments as outlined in the relevant [Schedule of Activities](#) located in the summary section.

The study also includes:

- QTc monitoring to evaluate the effect of PD-0332991 on QT interval via triplicate ECGs time-matched with select serial PK draws (subset study in at least 60 patients enrolled at selected sites);
- Quantification of trough PD-0332991 plasma concentration;
- A molecular profiling component aimed at assessing the relationship between breast tumor sensitivity and resistance to PD-0332991 and the alteration of cell cycle pathway-related genes and proteins in tumor tissues.

A total of 347 PFS events is required to have a 90% power to detect an improvement assuming a true hazard ratio equivalent to 44% improvement in median PFS over benchmark (single-agent letrozole PFS = 9 months) if tested at one-sided significance level of 0.025. The trial is designed to have one interim analysis for futility, efficacy, or possible sample size re-estimation planned after 65% (approximately 226 events) of expected PFS events have been observed using an Haybittle-Peto stopping boundary (for efficacy). The study is also powered for the secondary endpoint of overall survival (OS). An interim OS analysis will be performed at the time of the interim or final PFS analyses if the primary PFS analysis is positive.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

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

1. Adult women (≥ 18 years of age) with proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent and for whom chemotherapy is not clinically indicated.
2. Documentation of histologically or cytologically confirmed diagnosis of estrogen-receptor positive (ER+) breast cancer based on local laboratory results.
3. Previously untreated with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER+ disease.
4. Postmenopausal women defined as women with:
 - Prior bilateral surgical oophorectomy, **or**
 - Medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months or follicle-stimulating hormone (FSH) and estradiol blood levels in their respective postmenopausal ranges with no alternative pathological or physiological cause.
5. Measurable disease as defined per RECIST v.1.1 (see [Appendix 7](#)) or bone-only disease (with bone lesions confirmed by CT, MRI or bone X-ray). Tumor lesions previously irradiated or subjected to other locoregional therapy will only be deemed measurable if disease progression at the treated site after completion of therapy is clearly documented.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 (see [Appendix 1](#)).
7. Adequate organ and marrow function defined as follows:
 - ANC $\geq 1,500/\text{mm}^3$ ($1.5 \times 10^9 /\text{L}$);
 - Platelets $\geq 100,000/\text{mm}^3$ ($100 \times 10^9 /\text{L}$);

- Hemoglobin ≥ 9 g/dL (90 g/L);
 - Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 60 mL/min as calculated using the method standard for the institution;
 - Total serum bilirubin ≤ 1.5 x ULN (≤ 3.0 x ULN if Gilbert's disease);
 - AST and/or ALT ≤ 3 x ULN (≤ 5.0 x ULN if liver metastases present);
 - Alkaline phosphatase ≤ 2.5 x ULN (≤ 5.0 x ULN if bone or liver metastases present).
8. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).
9. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
10. All patients must agree to provide tumor tissues for centralized retrospective confirmation of ER status and to evaluate correlation between genes, proteins, and RNAs relevant to the cell cycle pathways and sensitivity/resistance to the investigational agents. Freshly biopsied, recurrent/metastatic tumor samples must be provided whenever possible. If such a biopsy is not feasible or cannot be safely performed, then an archived tumor sample may be accepted. In either case a formalin fixed, paraffin embedded (FFPE) block or 12 unstained FFPE slides are required for patient participation.
11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study before any study-specific activity is performed.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. HER2-positive tumor as defined by documentation of erbB-2 gene amplification by FISH (as defined by a HER2/CEP17 ratio ≥ 2) or chromogenic in situ hybridization (CISH, as defined by the manufacturer's kit instruction) or INFORM HER2 dual ISH (as defined by manufacturer's kit instruction) or documentation of HER2-overexpression by IHC (defined as IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory results utilizing one of the sponsor-approved assays (see [Appendix 2](#)). If HER2 status is unavailable or was determined using a test other than a sponsor-approved assay, then testing must be performed/repeated using one of these assays prior to randomization. If tissue sample from both primary and recurrent/metastatic tumors are available, HER2 assessment from the most recent sample (ie, recurrent/metastatic sample) should be used to define eligibility whenever feasible.

2. Patients with advanced, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement).
3. Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.
4. Prior neoadjuvant or adjuvant treatment with a non-steroidal aromatase inhibitor (ie, anastrozole or letrozole) with disease recurrence while on or within 12 months of completing treatment.
5. Prior treatment with any CDK4/6 inhibitor.
6. Patients treated within the last 7 days prior to randomization with:
 - Food or drugs that are known to be CYP3A4 inhibitors (ie, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice);
 - Drugs that are known to be CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort).
 - Drugs that are known to prolong the QT interval (see [Appendix 3](#)).
7. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to $\geq 25\%$ of bone marrow are not eligible independent of when it was received (see [Appendix 4](#)).
8. Diagnosis of any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
9. QTc > 480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP).
10. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (eg, hypocalcemia, hypokalemia, hypomagnesemia).

11. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.0 Grade ≥ 2 , atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.
12. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.
13. Known hypersensitivity to letrozole, or any of its excipients, or to any PD-0332991/placebo excipients.
14. Known human immunodeficiency virus infection.
15. Other severe acute or chronic medical or psychiatric condition 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.
16. Patients who are investigational site staff members or relatives of those site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.
17. Participation in other studies involving investigational drug (s) (Phases 1-4) within 2 weeks before randomization and/or during participation in the active treatment phase of the trial.
18. Recent or active suicidal ideation or behavior.

4.3. Randomization Criteria

- Patients will be randomized into the study provided they have satisfied all patient selection criteria.
- The investigators or their pre-specified designee will randomize eligible patients by interactive randomization technology (IRT) as described in the Study Reference Manual.
- At the time of randomization, information about patient demographics and stratification factors [ie, site of disease (visceral vs non-visceral), disease-free interval since the end of the (neo)adjuvant treatment to disease recurrence (de novo metastatic vs ≤ 12 months vs > 12 months), nature of prior (neo)adjuvant anti-cancer therapies (prior hormonal therapy vs no prior hormonal therapy)] will be requested.
- The central computerized system will provide the randomization number and treatment assignment.

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.

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

5. STUDY TREATMENTS

5.1. Allocation to Treatment

If the patient is found to be eligible for the study, she should be randomized using a centralized internet/telephone registration system no more than 4 business days before administration of the first dose of investigational product.

After a patient has provided written informed consent, has completed the necessary baseline assessments, and is found to be eligible for the study, the clinical site must complete a Patient Pre-Randomization Form which includes key eligibility criteria (eg, breast cancer diagnosis, stage of disease at initial diagnosis and at screening, hormonal receptor and HER2 status as per local results, prior systemic therapy, disease free interval (DFI) from prior (neo)adjuvant letrozole or anastrozole (if applicable)) and send it to the sponsor for approval of randomization. Upon receipt of the sponsor's approval the site must contact a centralized internet/telephone registration system as described in the Study Reference Manual, to enroll the patient on study (see [Section 4.3](#)).

Eligible patients will be randomly assigned in a 2:1 ratio to either Arm A (experimental arm: PD-0332991 plus letrozole) or Arm B (control arm: placebo plus letrozole) stratified according to site of disease, disease-free interval since completion of prior (neo)adjuvant therapy, and nature of prior (neo)adjuvant anti-cancer treatment received (see [Section 4.3](#)).

Clinical sites must complete the screening case report forms (CRFs) for all registered and randomized patients, even if the patient is not subsequently treated in this study.

At the time of registration, the clinical site staff must provide site and patient identifiers and demographic information. The IRT will assign a unique patient identification number. The IRT system will also be used to assign study medication.

If a patient does not receive the correct study treatment for their allocated treatment arm, the reason must be clearly documented in CRF. The patient will remain on study, baseline data will be collected and follow up will continue as described in the relevant [Schedule of Activities](#) table.

5.2. Breaking the Blind

At the initiation of the trial, the trial site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reason of patient safety. Blinding codes may also be broken after a patient discontinues treatment due to disease progression, as determined by the treating investigator using RECIST v.1.1 criteria, but only if deemed essential to allow the investigator to select the patient's next treatment regimen and after discussion and agreement with the sponsor. Code should not be broken in the absence of emergency situations or progressive disease as per RECIST v.1.1 (eg, in case of clinical deterioration, increase in tumor markers or any other evidence suggestive of disease progression but in the absence of RECIST-defined disease progression). When the blinding code is broken, the date and reason for unblinding must be fully documented in source documents and entered on the case report form. However, every effort should be made by the site staff to ensure that the treatment arm in which the unblinded patient is assigned is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

5.3. Drug Supplies

The investigational drug used in the course of this trial is PD-0332991/placebo. In addition, all patients will receive letrozole. All three medications will be supplied by the sponsor.

5.3.1. Formulation and Packaging

5.3.1.1. PD-0332991

PD-0332991 will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of PD-0332991 free base. The sponsor will supply the oral drug formulation to sites in HDPE bottles containing 75 mg, 100 mg, or 125 mg capsules. The capsules can be differentiated by their size and color (see below).

Table 1. PD-0332991/Placebo Capsule Characteristics

Dosage	Capsule color	Capsule size
75 mg	Sunset Yellow/Sunset Yellow	2
100 mg	Caramel/Sunset Yellow	1
125 mg	Caramel/Caramel	0

5.3.1.2. Placebo

Placebo will be indistinguishable from the PD-0332991 capsules and will be supplied as capsules matching in size and color the various PD-0332991 formulations (see [Table 1](#)). The sponsor will supply placebo to sites in HDPE bottles.

5.3.1.3. Letrozole

Commercially available letrozole 2.5 mg film-coated tablets will be supplied to sites by the sponsor. Complete information about letrozole formulation can be found in the UK Summary of Product Characteristics (SPC) for Femara.⁶⁶

5.3.2. Preparation and Dispensing

5.3.2.1. PD-0332991/Placebo

PD-0332991 will be provided in non-patient-specific bottles containing either 75 mg, 100 mg or 125 mg capsules. Matching placebo capsules will be provided in non-patient-specific bottles as to be indistinguishable from PD-0332991.

The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Returned unused medication **MUST NOT** be re-dispensed to patient.

PD-0332991/placebo is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only one capsule strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously dispensed medication to the clinic and new capsules will be dispensed.

5.3.2.2. Letrozole

Letrozole tablets will be provided in blister packs or in bottles with a safety screw cap.

The patient number should be recorded on the bottle/blister pack label in the spaces provided by site personnel at time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles/blister packs should be returned to the site at the next study visit.

5.3.3. Administration

5.3.3.1. PD-0332991/Placebo

Patients should be instructed to swallow PD-0332991/placebo capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day. Patients should be instructed to record daily administration of the study drugs in a patient diary.

PD-0332991/placebo will be administered together with letrozole. Patients should take PD-0332991/placebo with food. For patients enrolled in Group 1, patients should fast from 1 hour before to 2 hours after dosing, during Cycle 1. Cycle 2 and beyond, patients should take PD-0332991/placebo with food.

PD-0332991/placebo will be administered orally once a day for 21 days of every 28-day cycle followed by 7 days off treatment. In the event the Day 1 clinic visit of the subsequent cycle is scheduled during the -2 day allowable visit time window (ie, Day 27, Day 28), patients must be instructed to complete their 7-day off treatment period of the current cycle prior to resuming blinded therapy even if criteria for treatment resumption are met at the visit. Cycle off treatment periods of less than 7 days are considered protocol deviations.

Patients experiencing investigational product related toxicity may have their dose modified according to [Section 5.3.4](#).

5.3.3.2. Letrozole

Letrozole will be administered orally once daily continuously together with PD-0332991/placebo or alone in the event of PD-0332991/placebo dosing interruption.

Refer to the UK Summary of Product Characteristics (SPC) for Femara⁶⁶ for additional administration instructions.

5.3.3.3. General Rules

For both PD-0332991/placebo and letrozole:

- Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.
- Patients who vomit anytime after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.

Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose. Also refer to [Section 5.3.5](#) for further details on medication errors and overdose.

5.3.4. Dose Modification

A Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of study drugs (PD-0332991/placebo or letrozole) may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, dosing adjustment may be required for just one or both study drugs in the combination. In the event treatment interruption is deemed necessary for just one of the study drugs in the combination, treatment with the other study drug will continue as planned.

5.3.4.1. Letrozole

No dose adjustment for letrozole is permitted but dosing interruptions are allowed. Treatment interruption for letrozole-related toxicities will be performed as per the investigator's best medical judgment.

Patients discontinuing letrozole treatment due to treatment-related toxicity will be discontinued from the active treatment phase of the study and enter the follow-up phase.

5.3.4.2. PD-0332991/Placebo

In the event of significant treatment-related toxicity, PD-0332991/placebo dosing may be interrupted or 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 sign or symptom.

Dose modifications may occur in 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.

Patients discontinuing PD-0332991/placebo treatment due to treatment-related toxicity may continue on the active treatment phase of the study receiving letrozole monotherapy as per the investigator's discretion.

5.3.4.2.1. Dosing Interruptions

Patients experiencing the following adverse events should have their treatment interrupted/delayed:

- Uncomplicated Grade 3 neutropenia ($ANC < 1000/mm^3$);

- Grade 3 neutropenia ($ANC < 1000/mm^3$) associated with a documented infection or fever $\geq 38.5^\circ C$;
- Grade 4 neutropenia ($ANC < 500/mm^3$);
- Grade 4 thrombocytopenia (Platelet count $< 25,000/mm^3$);
- Grade ≥ 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment);
- Grade 3 QTc prolongation (QTc ≥ 501 msec on at least two separate ECGs).

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 [Section 5.3.4.2.2](#).

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 [Section 5.3.4.2.3](#) Dose Reductions 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, non-cancer related surgery) lasting > 2 weeks, treatment resumption will be decided in consultation with the sponsor.

5.3.4.2.2. Dose Delay

Retreatment 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:

- Platelet count $\geq 50,000/mm^3$;
- $ANC \geq 1000/mm^3$ and no fever;
- Grade 3 or higher treatment-related non-hematologic AEs (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), with the exception of alopecia, have recovered to Grade ≤ 1 or baseline (or, at the investigator's discretion, Grade ≤ 2 if not considered a safety risk for the patient).

- QTc <501 msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, ECG should be monitored more frequently as per the investigator's best medical judgement until QTc ≤ 480 msec.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be increased as clinically indicated.

If these parameters are met within 2 weeks of treatment interruption or cycle delay, PD-0332991/placebo may be resumed. Please refer to [Section 5.3.4.2.3](#) Dose Reductions for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 2 weeks of dosing interruption (including the scheduled 1 week off treatment) or 2 weeks of cycle delay, permanent discontinuation of PD-0332991/placebo treatment should be considered. Treatment resumption for patients recovering from treatment-related toxicity after >2 weeks of treatment interruption or cycle delay but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment is left at the investigator's discretion.

A new cycle only starts when the criteria listed above are met and blinded study treatment may be administered, otherwise initiation of the new cycle must be delayed until such criteria are met.

In the event that the start of a new cycle is delayed due to treatment related toxicity, procedures required on Day 1 of the given cycle will be performed when PD-0332991/placebo is resumed. New cycle Day 1 procedures (ie, physical examination, ECOG performance status, ECG, Quality of Life questionnaires, blood chemistry, hematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.

5.3.4.2.3. Dose Reductions

Following dosing interruption or cycle delay the PD-0332991/placebo dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Dose reduction of PD-0332991/placebo by 1 and, if needed, 2 dose levels ([Table 2](#)) will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from the study and entered into the follow-up phase. All dose modifications/adjustments must be clearly documented in the patient's source notes and Investigational product administration 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. Dose re-escalation is not allowed.

Table 2. Available Dose Levels

Dose Level	PD-0332991/Placebo for 3 out of 4 weeks (3/1 schedule)	Letrozole on a continuous daily dosing regimen
Starting dose	125 mg/d	2.5 mg/d
-1	100 mg/d	2.5 mg/d
-2	75 mg/d*	2.5 mg/d
Discontinue Study Treatment		

* PD-0332991/placebo dose de-escalation below 75 mg/d is not allowed.

PD-0332991/placebo recommended dose modifications for treatment related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 3.

Table 3. D-0332991/Placebo Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment.

Toxicity	Restart PD-0332991/Placebo Treatment at:
Uncomplicated Grade 3 neutropenia ($ANC < 1000/mm^3$)	Same dose level
Grade 3 neutropenia ($ANC < 1000/mm^3$) associated with a documented infection or fever $\geq 38.5^\circ C$	↓ 1 Dose Level
Grade 4 neutropenia ($ANC < 500/mm^3$)	↓ 1 Dose Level
Grade 4 thrombocytopenia ($Platelet\ count < 25,000/mm^3$)	↓ 1 Dose Level
Grade ≥ 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)	↓ 1 Dose Level

QTc prolongation management

In the event of QTc prolongation of, possible alternative reversible causes such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval should be evaluated.

If such reversible causes are identified, then they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval).

Recommended dose modifications in the event of QTc prolongation are provided in [Table 4](#).

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Table 4. PD-0332991/Placebo Dose Modifications in the Event of QTc Prolongation

	Toxicity (NCI CTC Grade, Version 4.0)		
	Grade 2 QTc prolongation	Grade 3 QTc prolongation	Grade 4 QTc prolongation
Reversible cause identified	Treat reversible cause Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the <u>same dose level</u> ⁽¹⁾	Treat reversible cause Withhold treatment until QTc<501 msec Resume treatment at the <u>same dose level</u> . Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec.	Permanently discontinue
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the <u>same dose level</u> ⁽¹⁾	Withhold treatment until QTc<501 msec Resume treatment at the <u>next lower dose level</u> ⁽²⁾ Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec.	Permanently discontinue

1. If the QTc remains above 480 msec more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the emerging safety data from PD-0332991 trials and the investigator's best medical judgment.
2. If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be discussed with study medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from PD-0332991 trials and the investigator's best medical judgment.

5.3.5. Medication Errors and Overdose

Medication errors may result in this study from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page and on the serious adverse event (SAE) form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- 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.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated adverse event(s) are captured on an adverse event (AE) CRF page.

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5.3.6. Compliance

Patients will be required to return all bottles of PD-0332991/placebo and all blisters/bottles of letrozole as well as the completed patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. The number of remaining capsules/tablets will be documented and recorded.

To be considered compliant, each study patient must have received at least 80% of the planned number of doses of primary therapy based on the number of days of actual dose administration. Dose adjustments must follow instructions provided in the [dose adjustment guidelines](#) section.

5.4. Drug Storage and Drug Accountability

Storage conditions stated in the Study Reference Safety Document (ie, Investigator's Brochure (IB), United States Package Insert (USPI), Summary of Product Characteristics (SPC), or Local Product Document (LPD)) may be superseded by the label storage.

Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of investigational products (See [Sections 5.4.1 & 5.4.2](#)). These include thermometers for both the room storage and refrigerator storage. Any temperature excursions must be reported immediately to the sponsor and documented. Once a deviation is identified, the investigational products (PD-0332991/placebo or letrozole) MUST be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

At the end of the trial, or at the close-out of the site, the site will destroy any unused investigational product.

If the destruction occurs at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor. Destruction must be adequately documented. Alternatively, investigational product may be shipped to a local depot for destruction.

5.4.1. PD-0332991/Placebo

PD-0332991/placebo capsules should be stored at controlled room temperature (15-30°C, 59-86°F) in their original container.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, PD-0332991/placebo capsules will be accounted for as instructed by the sponsor. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

5.4.2. Letrozole

Letrozole tablets must be stored according to the instructions detailed in the local package insert.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, letrozole tablets will be accounted for as instructed by the sponsor. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

5.5. Concomitant Medications

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. Any medications including herbal supplements, vitamins, or treatment taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of investigational product and the reason for their administration must be recorded on the CRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anesthesia" on the concomitant treatment records; it is not necessary to list the specific anesthetics. Palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

5.5.1. Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **Anti-cancer agents:** No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than letrozole will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on study.

- **Strong/Moderate CYP3A inhibitors/inducers:** PD-0332991 is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, PD-0332991 is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are strong CYP3A inhibitors or inducers may change the plasma concentrations of PD-0332991 in humans. The concurrent use of the compounds listed below is not allowed in the study:
 - Strong CYP3A inhibitors, including boceprevir, clarithromycin, conivaptan, delavirdine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.
 - The following moderate CYP3A inhibitors: amprenavir, atazanavir, diltiazem, erythromycin, fosamprenavir, and verapamil.
 - Strong CYP3A inducers, including carbamazepine, phenytoin, primidone, rifampin, rifapentin, and St. John's wort.
 - The following moderate CYP3A inducers, felbamate, nevirapine, phenobarbital, and rifabutin.
- **Drugs known to cause QT interval prolongation** are prohibited during the active treatment phase. Refers to [Appendix 3](#) for a list of drugs known to predispose to Torsade de Pointes.
- **Hormone replacement therapy**, topical estrogens (including any intra-vaginal preparations), **megestrol acetate** and **selective estrogen-receptor modulators** (eg, raloxifene) are prohibited during the active treatment phase.
- **Proton-pump inhibitors:** the concomitant use of proton-pump inhibitors (including, but not limited to, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) with PD-0332991/placebo is prohibited. Further recommendations about the use of antacids are provided under [Section 5.5.3](#).

The strong/moderate CYP3A inhibitors/inducers and proton-pump inhibitors listed above are permitted for any patients who permanently discontinue blinded therapy and continue on trial with letrozole monotherapy only.

5.5.2. Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the sponsor is required prior to treatment initiation.

The concurrent use of dexamethasone is not recommended.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.

The use of **herbal medicine** is not recommended during the active treatment phase.

5.5.3. Permitted Medications

The following treatments are permitted throughout the duration of the active treatment phase:

- **Standard therapies** for pre-existing medical conditions, medical and/or surgical complications, and palliation. Any medication intended solely for supportive care (eg, analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion. All medications should be recorded.
- **Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors** for the treatment of osteoporosis or management of existing bone metastases may be continued for patients who have been receiving them at a stable dose for at least 2 weeks prior to randomization. However the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of patient from the active treatment phase unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the subject's source documentation.
- **Hematopoietic growth factors** (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Primary prophylactic use of granulocyte-colony stimulating factors is not permitted but they may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guideline.⁷¹ If neutropenic complications are observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered to be a reasonable alternative.
- **Erythropoietin** may be used at the investigator's discretion for the supportive treatment of anemia.
- **Local antacids** may decrease PD-0332991 absorption and exposure; however, if needed, local antacid should be given at least 2 hours before or after PD-0332991/placebo administration.
- **H₂-receptor antagonists** (including, but not limited to, cimetidine, famotidine, nizatidine, ranitidine). The dosing of PD-0332991/placebo should occur at least 10 hours after H₂-receptor antagonist evening dose and 2 hours before H₂-receptor antagonist morning dose.

5.6. Concomitant Radiotherapy or Surgery

Any concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery are prohibited throughout the duration of the active treatment phase of the study. Patients requiring any of these procedures will be discontinued from the active treatment phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PD-0332991 with radiotherapy, PD-0332991/placebo treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after. For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (eg, lesions at risk for spontaneous micro-fractures or painful lesions). Palliative radiotherapy during the active treatment phase will be considered alternative cancer therapy and will result in censoring of the PFS endpoint. The dates on which palliative radiotherapy is administered should be recorded on the appropriate CRFs.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PD-0332991 required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping PD-0332991/placebo is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinstitute PD-0332991/placebo treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

Prior to undergoing any study specific procedures (with the exception of certain imaging assessments if meeting the criteria defined in Section 6.1), patients must read and sign the consent form. All study procedures and the timing when they must be performed are detailed in the [Schedule of Activities](#) tables. All data obtained for these assessments must be supported in the patients' source documentation.

For the purposes of this trial, 1 cycle is 28 days. A cycle could be longer than 28 days if persistent toxicity delays the initiation of the subsequent cycle.

6.1. Screening

Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed (with the exception of certain imaging assessments if meeting the criteria defined in this section); however, it may be obtained more than 28 days before randomization.

Radiographic tumor assessments (as documented on the [Tumor Assessment Requirement Flowchart](#)) that were performed before the signing of the informed consent form as routine procedures (but within 28 days prior to randomization) do not need to be repeated and may be used as baseline assessments, as long as:

- The tests were performed per the method requirements outlined in the [Tumor Assessment Requirement Flowchart](#), the [Efficacy Assessments](#) sections.
- Appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

Bone scans performed as routine procedures within 12 weeks prior to randomization may also be accepted as baseline assessment if they meet the same requirements listed above.

Brain scans performed as routine procedures within 6 weeks prior to randomization may also be accepted as baseline assessment if they meet the same requirements listed above.

Once Amendment 3 is IRB approved, all lens grading evaluable, newly enrolled patients will undergo the following ophthalmic procedures at baseline:

- Best corrected distant visual acuity (Snellen).
- Refractive error associated with best corrected distant visual acuity.
- Intraocular pressure (IOP - one reading).
- Slit lamp biomicroscopy of the anterior segment including cell count and flare grading.
- Lens grading with the Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedures using a laminated reference pocket card (See [Appendix 8](#)) - (pupil dilated examination).
- Funduscopy (Ophthalmoscopy - pupil dilated examination).

Patients with ophthalmic conditions (eg, anophthalmus, phthisis, aphakia, pseudophakia) that would prevent grading of the lens in both eyes will not be considered evaluable for this ophthalmic assessment and do not need to undergo these ophthalmic procedures. Reasons for not being evaluable must be clearly documented in the patient source notes.

All ophthalmic examinations will be performed by an ophthalmologist. Refer to [Section 7.2.3](#). Ocular Safety Assessments for further details on these procedures.

For details on baseline procedures, see the [Schedule of Activities](#) tables.

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6.1.1. Screen Failure

Patients who completed the informed consent process but do **NOT** meet all eligibility criteria and therefore are **NOT** randomized to either treatment arm will be considered as screen failures.

Clinical sites must provide for all screen failures the following information using the appropriate case report forms (CRFs): screening number, demographic data as well as the final subject summary including the reason for screening failure.

6.2. Active Treatment Phase

For details on procedures during the active treatment phase, see the [Schedule of Activities](#) tables.

In the event that the start of a new cycle is delayed due to treatment-related toxicity, procedures required on Day 1 of the given cycle will be performed when PD-0332991/placebo is resumed. New cycle Day 1 procedures (ie, physical examination, ECOG performance status, ECG, Quality of Life questionnaires, blood chemistry, hematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.

All lens-grading evaluable patients randomized under Amendment 3 will repeat screening ophthalmic procedures also during the active treatment phase after 3 months (Cycle 4 Day 1), 6 months (Cycle 7 Day 1), 12 months (Cycle 13 Day 1) then every 12 months (Day 1 of Cycles 25, 37, etc...) thereafter. Additional ophthalmic examinations may be repeated during the study as clinically indicated (including for patients randomized prior to Amendment 3 approval).

6.3. End of Treatment Visit

The end of treatment visit will be performed as soon as possible but no later than 4 weeks (ie, 28 days) \pm 7 days from last dose of investigational product and prior to the initiation of any new anti-cancer therapy.

All lens-grading evaluable patients randomized under Amendment 3 will repeat screening ophthalmic procedures also at the End of Treatment visit.

For details on procedures to be performed at the End of Treatment visit, see the [Schedule of Activities](#) tables.

6.4. Follow-up Visit

After discontinuation of study treatment, the following follow-up activities will be required:

- Post-study survival status and information related to post-study anti-cancer therapies (including regimen number / name of post-study anti-cancer therapy, start/stop dates, and dates of disease progression on subsequent anti-cancer therapies) will be collected approximately every 6 months (± 7 days) from the last dose of investigational product until patient permanent discontinuation from study or end of follow-up period whichever occurs first. Telephone contact is acceptable.
- In addition, post-study breast cancer specific quality of life questionnaire (FACT-B) will also be collected every 6 months (± 7 days) from the last dose of investigational product until patient permanent discontinuation from study or end of follow-up period whichever occurs first. During the follow-up period, all self-assessment questionnaires should preferably be completed by the patients during a scheduled clinic visit. However, if no clinic visits are being scheduled during the follow-up period interviewer administration via phone call may be used instead and documented accordingly in the patient source notes.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST definitions will continue to have tumor assessment performed during the follow-up visits every 12 weeks (± 7 days) and bone scans (as applicable) every 24 weeks (± 7 days) from the date of randomization until disease progression, initiation of new anti-cancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

For details on follow-up visit procedures, see the [Schedule of Activities](#) tables.

6.5. Patient Withdrawal

6.5.1. Active Treatment Phase Discontinuation

The term "interruption" refers to a patient stopping the investigational product during the course of the study, but then re-starting it at a later time in the study. The reason for dosing interruption will be collected on the appropriate CRF.

The term "discontinuation" refers to a patient's withdrawal from the active treatment phase. The reason for discontinuation from treatment will be collected on the appropriate CRF.

Patients may be withdrawn from the active treatment phase in case of:

- Disease progression as per RECIST v.1.1;
- Symptomatic deterioration (ie, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression as per RECIST v.1.1);

- Need for additional anti-cancer therapy not specified in the protocol;
- Unacceptable toxicities;
- Investigator conclusion that it is in the patient's best interest to discontinue therapy (eg, poor compliance with either protocol monitoring or with taking the study medications, etc);
- Lost to follow-up*;
- Patient choice to withdraw from treatment (follow-up permitted by patient);
- Withdrawal of patient consent (cessation of follow-up);
- Death.

*If a patient does not return for a scheduled visit, every effort should be made to contact the patient. If after 3 unsuccessful attempts to contact the patient, one of which is by registered letter, the patient should be considered "lost to follow-up". Steps taken to contact the patient (eg, dates of telephone calls, registered letters, etc) must be clearly documented in the source documents.

Patient who discontinue from the active treatment phase must have end of treatment/withdrawal evaluations performed as soon as possible but no later than 4 weeks from the last dose of investigational product and prior to initiation of any new anti-cancer therapy. Data to be collected for the end of study treatment/withdrawal are described in the [Schedule of Activities](#) tables.

If a patient opts to discontinue from the active treatment phase as a result of an unacceptable adverse drug reaction, "withdrawal of consent" should not be the reason for discontinuation. Instead, the reason for discontinuation of active treatment phase, must be recorded as "Unacceptable toxicity" and an appropriate action taken must be assigned on the AE CRF to the adverse event leading to the patient's withdrawal of consent.

6.5.2. Study Discontinuation

Patients may withdraw from the study 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 or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Patients will be withdrawn from study in the case of:

- Withdrawal of consent (ie, refuses tumor assessments or survival status after end of treatment);
- Lost to follow-up;*
- Death.

*If a patient does not return for a scheduled visit, every effort should be made to contact the patient. If after three unsuccessful attempts to contact the patient, one of which is by registered letter, the patient should be considered “lost to follow-up”. Steps taken to contact the patient (eg, dates of telephone calls, registered letters, etc) must be clearly documented in the source documents. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

Data to be collected for the end of study treatment/withdrawal are described in the [Schedule of Activities](#) tables.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further 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

All study procedures are described in the [Schedule of Activities](#) tables footnotes.

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 which he/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 fashion.

7.1. Efficacy Assessments

7.1.1. Independent Review of Disease Assessments

A blinded independent third-party core imaging laboratory will perform a retrospective review of radiographic images and clinical information collected on-study to verify the protocol defined endpoints of disease response and progression as assessed by the investigator.

It is important to the integrity of the study that all imaging studies and clinical information (including photographs) are forwarded to the independent core imaging laboratory as each patient enrolls and progresses through the study.

Materials to be forwarded for independent review are the following:

- All imaging studies performed on study, preferably in digital format on compact disc or optical disc. All digital media must be in DICOM format. Films may be forwarded for review if necessary; all films must be originals (second original films acceptable) rather than copies of films.
- Photographs of sites of disease assessed using clinical methods. Details concerning clinically assessed lesions will be collected on the CRFs and made available to the core imaging laboratory.

Further information on materials to be forwarded for independent review, correct procedures for the coding/blinding of the patient's name/identity and the return of the source data/documents to the site is provided in the core imaging laboratory Study Coordinator Manual.

7.1.2. Tumor Assessments

The importance of timely and complete disease assessments in this study cannot be understated. Disease assessments must be performed as scheduled according to the calendar, regardless of treatment delays resulting from toxicity, to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. A series of incomplete disease assessments will result in censoring of the primary endpoint of PFS back to the time of the last full assessment that did not show progression. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

Screening/baseline tumor assessment will be carried out within 28 days of randomization (unless otherwise specified below).

- Disease assessment for all patients at baseline will include:
 - CT or MRI scan of the chest, abdomen, and pelvis (CAP).
 - CT or MRI scan of any other sites of disease as clinically indicated.
 - Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.

- Bone scans in order to detect bony sites of disease. Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline must be confirmed by X-ray, CT scan with bone windows or MRI. Bone lesions identified at baseline will follow the same assessment schedule as for measurable lesions. Baseline brain CT or MRI are only required in case signs and symptoms suggest the presence of metastatic brain disease. Refer to [Section 6.1](#) for further details on timing allowance for baseline brain and bone scans.

Post-baseline tumor assessments will be performed every 12 weeks (± 7 days) and bone scans (as applicable) every 24 weeks (± 7 days) from randomization until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anti-cancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up). Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST definitions will continue to have tumor assessment performed during the follow-up visits every 12 weeks (± 7 days) and bone scans (as applicable) every 24 weeks (± 7 days) until documented disease progression, initiation of new anti-cancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Every effort should be made to perform a last tumor assessment before starting a new anti-cancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.

Post-baseline tumor assessments will include:

- CT or MRI scan of the chest, abdomen, and pelvis (CAP).
- CT or MRI scan of any other sites of disease identified at baseline.
- Clinical assessment of sites of superficial disease identified at baseline. Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.
- Bone lesions imaging:
 - If bone lesions were identified at baseline the following assessment must be performed:

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- X-ray/CT scan/MRI every 12 weeks (± 7 days) from the date of randomization using the same modality used to confirm the bone lesions at baseline. Areas that have received palliative radiotherapy on study cannot be used to assess response to study treatment.
- Bone scans every 24 weeks (± 7 days) from the date of randomization and to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.
- If no bone lesions were identified at baseline, bone scans should be performed as clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.
- Repeat brain scans will be required only if metastases are suspected.

The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease.

However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF).⁷³

The same method and technique should be used to characterize each lesion identified and reported at baseline, during the study treatment period and during follow-up. The use of plain-film X-rays (with the exception of bone X-rays as detailed above) is discouraged. The use of positron emission tomography (PET) imaging as the only imaging modality is not permitted.

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

Objective tumor response will be measured using the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1, see <http://www.eortc.be/recist/default.htm>). Also please refer to [Appendix 7](#). All measurements should be recorded in metric notation using a ruler or calipers.

For patients with bone-only disease:

- Treatment outcome will be recorded in the CRF as complete response (CR), stable disease (SD) or progression (PD).

Interpretation will be PD if:

- The malignant nature of one or more new lesions identified with bone scan is confirmed with X-ray, or CT, or MRI scan,
- Flare observed in bone scan is followed by confirmation of progression with other imaging modalities,
- Clinical worsening of the disease is assessed by bone scan and disease progression (ie, new lesion(s)) is confirmed with other imaging modalities.
- Unequivocal progression of existing bone lesions.

Interpretation will be SD if:

- The malignant nature of all the new lesions identified with bone scan is not confirmed.

In the following cases the patient will be censored at the date of prior tumor assessment with no PD: 1) on-study fracture; 2) on-study management of pain (palliative radiation therapy, palliative surgery), 3) clinical worsening not objectively confirmed; 4) on-study change of therapy. In all the censored cases (no objectively documented PD) tumor assessment will be performed until PD. Also, it will be at the discretion of the investigator to discontinue the study treatment.

It is suggested to institute palliative radiotherapy (eg, lesions at risk for spontaneous micro-fractures or painful lesions) before study initiation as well as palliative surgery if possible and clinically appropriate.

7.1.3. Overall Survival

Following the End of Treatment visit, survival status will be collected in all patients (telephone contact is acceptable) every 6 months (± 7 days) from the last dose of study treatment. Information on subsequent anti-cancer therapy will also be collected (See [Section 6.4](#)).

7.2. Safety Assessments

Safety assessment will consist of monitoring of all adverse events (AEs), including serious adverse events (SAEs), regular monitoring of hematology, serum chemistry, and routine monitoring of ECGs, physical examinations, vital signs, ECOG performance status, and chest CT scans.

Adverse event assessment will include type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 4.0, see [Severity Assessment](#) section), timing, seriousness, and relatedness.

Baseline tumor-related signs and symptoms will be recorded at the Cycle 1 Day 1 visit and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

7.2.1. Laboratory Safety Assessments

Blood tests will include the following:

Hematology Panel		Blood Chemistry Panel	
1	Hemoglobin	1	ALT
2	Platelets	2	AST
3	WBC	3	Alkaline Phosphatase
4	Absolute Neutrophils	4	Sodium
		5	Potassium
		6	Total Calcium
		7	Magnesium
		8	Total Bilirubin
		9	BUN or Urea
		10	Serum Creatinine
		11	Albumin
		12	Hemoglobin A1c

Blood tests will be drawn at the time points described in the [Schedule of Activities](#) table, and analyzed at local laboratories. Additional blood tests may be performed at the investigator's discretion as clinically indicated for the purpose of planning treatment administration, dose modification, or following adverse events.

7.2.2. Electrocardiogram (ECG)

All ECGs will be performed using a 12-lead (with a 10-second rhythm strip) tracing. ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

ECG interval readings by the ECG recorder's algorithm will be read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents.

Triplicate ECGs (referred as ECG_E) will be performed for all patients to determine the mean QTc interval for eligibility purpose.

Patients found to be eligible will be part of one of the two groups highlighted below depending on which site screened the patient. ECG frequency for each group is described below:

- Patients in Group 1 (approximately 60 patients) will be enrolled at selected sites and will have their QTc monitored to evaluate the effect of PD-0332991 on QT interval via serial triplicate ECGs time-matched with PK draws. ECGs will be obtained on the day preceding treatment initiation (Day 0) at time 0 (time of first ECG also referred to as ECG1) and then 2, 4, 6, and 8 Hrs after ECG1, and on Day 14 of Cycle 1 pre-dose (0 Hrs) and 2, 4, 6, and 8 Hrs following PD-0332991 administration. Timing of ECGs performed on Day 14 MUST be time-matched (clock time \pm 35 minutes) with ECG assessments performed on Day 0 (eg, if the ECG1 on Day 0 was performed at 10:00 AM then the 0 hour triplicate ECGs on Day 14 must be performed within the 9:30 AM - 10:30 AM timeframe but as close as possible to 10:00 AM whenever feasible). On Day 14 of Cycle 1, study treatment should be administered immediately after the pre-dose PK draw has been collected. **All ECGs should be obtained after a fast of at least 1 hour.** ECGs should be performed immediately before PK blood draws at respective time points. Patients who cannot complete ECG measurements on Day 0 and/or PK-matched ECG measurements (both ECG and PK collected) on Day 14 will need to be replaced. Additionally, triplicate ECGs will be obtained for safety monitoring at 0 hour (pre-dose) on Day 1 of Cycle 1*, Day 14 of Cycle 2, then on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 will be performed as clinically indicated.
- Patients in Group 2 (all other patients) will have triplicate ECGs performed for safety monitoring at 0 hour (pre-dose) on Day 1 of Cycle 1*, Day 14 of Cycles 1 and 2, then on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 will be performed as clinically indicated. **All ECGs should be obtained after a fast of at least 1 hour.**

*Note: Triplicate ECGs do not need to be repeated on Day 1 of Cycle 1 if ECG_E was performed within 7 days of the date of randomization.

Additional ECGs may be performed as clinically indicated at any time.

For the purpose of the study, triplicate ECGs are defined as three consecutive ECGs performed approximately 2 minutes apart but within 10 minutes for all 3 ECGs at the protocol specified timepoints (see [Schedule of Activities](#) table for details) to determine the mean QTc interval. All triplicate ECG tracings will be sent electronically to a core ECG laboratory for blinded manual interval measurements. The blinded manual interval measurements from the core ECG laboratory will be used for primary statistical analysis of ECG data in Group 1 patients.

If at any time during the course of treatment, the mean QTc is prolonged (≥ 501 msec on at least two separate ECGs, ie, CTCAE Grade ≥ 3), 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 confirms a QTc of

≥501 msec, immediate search for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 501 msec.

- If QTc interval reverts to less than 501 msec, and in the judgment of investigator(s) in consultation with the sponsor the cause is determined to be other than study drug, treatment may be continued with regular ECG monitoring under hospital supervision.
- If in that timeframe the QTc intervals remain above 501 msec the study drug will be held until the QTc interval decreases to <501 msec.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, 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 investigational product causality cannot be ruled out, Investigational product dose adjustment and/or discontinuation should be performed according to instructions provided in [Section 5.3.4: Dose Modification](#). Additional triplicate ECGs may be performed as clinically indicated.

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

7.2.3. Ocular Safety Assessments

7.2.3.1. Snellen Best Corrected Visual Acuity and Refraction

Snellen visual acuity will be assessed by using a standard wall or projection chart before implementing any procedures that can affect vision (eg, pupil dilation, tonometry, and gonioscopy). The same optotype will be used throughout the study for a specific patient, and the right eye should be tested first. The refractive error will be determined at the Screening visit. The examiner should ensure that patients are seated comfortably and that they do not move their head forward or backward during testing. Patients will be told that the chart contains only letters.

The line read with 2 or fewer errors will be recorded. If 3 of the 5 letters on a line are read correctly, the patient will be given credit for that line. For example, if the patient reads 20/25 +3, 20/20 will be recorded.

A decrease in best-corrected visual acuity of 3 lines or more from the Screening visit will be reported as an adverse event. An adverse event of visual acuity will be counted from the following lines: 20/20 or better, 20/25, 20/30, 20/40, 20/50, 20/60, 20/70, 20/80, 20/100, 20/125, 20/150, and 20/200. If the acuity at screening is better than 20/20, the decrease will be calculated from 20/20.

In the event of a decrease in visual acuity of 3 lines or more from screening, refraction will be rechecked at all subsequent study visits. A change in refraction power (spherical or cylindrical) of ± 1.25 diopters compared with the screening examination will be reported as an adverse event.

7.2.3.2. Intraocular Pressure Measurement

Intraocular pressure (IOP) will be measured using a calibrated Goldmann applanation tonometer. Both eyes will be tested, with the right eye preceding the left eye. The operator will initially set the dial at 10 mm Hg, then look through the slit lamp and adjust the dial to take the reading, and then record the results, including the time assessment is made.

Any IOP increase of greater than 10 mmHg **above baseline** or any IOP that increases above 25 mm Hg will be reported as an adverse event (AE).

7.2.3.3. Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy with fluorescein will be performed. At each scheduled visit, deposition of pigment on the corneal endothelial layer or the lens capsule or any abnormalities of the lids, conjunctivae, cornea, anterior chamber, iris, or lens (see [Lens Grading](#)) will be graded as mild, moderate, or severe. Slit-lamp biomicroscopy should precede IOP measurement and the administration of any pupil-dilating agent for ophthalmoscopy.

Cells and flare in the anterior chamber should be noted during the slit-lamp examination.

Intraocular Inflammation Grading Scale for Biomicroscopy:

	Grade				
	0	1	2	3	4
Grading of aqueous flare	Completely Absent	Barely Detectable	Moderate (iris and lens details clear)	Marked (iris and lens details hazy)	Intense (formed fibrin in aqueous)
Grading of cells in the aqueous ^{a,b}	No cells	1 to 5 cells	6 to 10 cells	11 to 20 cells	>20 cells

^a Evaluation of Anterior Chamber Inflammation:

1. Examination of the anterior chamber for cells must be performed before either dilation or applanation tonometry.
2. The light intensity of the slit lamp is turned to the maximum tolerated by the patient.
3. High magnification and 1 x 2 mm slit are used.
4. The ray of light as directed at an angle of approximately 45° to the plane of the iris.

^b Modified from Hogan et al. 1959.⁷⁴

During the study, any new finding or deterioration from baseline findings should be reported as an adverse event.

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7.2.3.4. Lens Grading

When doing lens grading, graders must be aware of their bias, either conscious or unconscious, that cataract is a unidirectional disease that steadily gets worse with age. Because of this bias, if one knows the baseline or any prior lens grade, it is likely that the grade assigned at a follow-up visit will be higher. To avoid this potential observation bias, the grader will remain masked to earlier lens grading and should always start with a blank case report form (CRF). The Wisconsin AREDS 2008 Clinical Lens Opacity Grading Procedure will be used.⁷² Once the pupils are dilated to at least 5 mm, use slit lamp with ~10X magnification and brightest beam intensity.

- Nuclear opacity.
 - Orient beam at 45° to viewing axis.
 - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width.
 - Compare opalescence of nucleus with those on the provided pocket card of standard photos.
- Cortical and Posterior Subcapsular Cataract (PSC) opacities.
 - Select wide slit beam setting optimum for retro-illumination of lens.
 - Visualize lens opacities against red fundus reflex background.
 - Count only opacities definitely visible against red reflex.
 - Mentally combine all cortical opacities into one contiguous area.
 - Compare total opacity area with those on the provided pocket card of standard photos.
- Grade each type of opacity in half steps from <1 to >3 (1=mild, 2=moderate and 3=severe) using the scale defined on the provided pocket card of standard photos.

7.2.3.5. Funduscopy (Ophthalmoscopy)

Funduscopy (Ophthalmoscopy) will be performed after dilation of the pupils to examine the vitreous body, retina, and optic nerve head. At screening, any abnormalities and pathologic findings will be graded as mild, moderate, or severe.

Any new findings or deterioration from baseline findings will be reported as an adverse event.

7.2.4. Other Safety Assessments

A full physical examination including an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at screening only), weight, blood pressure and pulse rate which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening, and Day 1 of Cycles 1 and 2.

Symptom directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.

Performance Status: The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used (see [Appendix 1](#)).

7.3. Pharmacokinetic Assessments

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, samples obtained within 10 min or 10% of the nominal time AND collected prior to administration of the investigational product on that day (with the exception of the planned post-dose samples that will be collected on Day 14 of Cycle 1) 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 and safety assessments (ie hematology, blood chemistry, and ECGs) have been completed. The exact time of the sample collection and the most recent dosing time will be recorded on the CRF. The date of missing dose should also be recorded in the CRF.

One 3 mL sample of venous blood will be collected in appropriately labeled K2 EDTA collection tubes for assessment of PD-0332991 (including its active metabolites, if appropriate) levels at the protocol-specified times. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Blood samples will be collected from all participating patients for PK assessments of PD-0332991 on Day 14 of Cycles 1 and Cycle 2 before administration of investigational product on that day. In the event a pre-dose sample cannot be/is not collected on Day 14 of Cycle 1 or Cycle 2 as scheduled, every effort should be made to collect a makeup pre-dose sample between Day 15 and Day 21 of the same cycle or between Day 14 and Day 21 of any subsequent cycles beyond Cycle 2 following the same rules described above.

For patients participating in the dedicated QTc portion of the trial (Group 1), all PK draws at Day 14 of Cycles 1 and 2 will be done immediately after triplicate ECGs have been performed so that the PK samples are collected at the nominal time.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

As part of understanding the pharmacokinetics of the PD-0332991, blood samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report.

Refer to the Study Manual for detailed collection, processing and shipping procedures.

7.4. Patient Reported Outcomes

Patient reported outcomes of health-related quality of life and health status will be assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) and EuroQol-5D (EQ-5D) instruments.

The FACT-B and EQ-5D will be given to the patient in the appropriate language for the site.

Patients will complete each instrument pre-dose on Day 1 of Cycle 1 through 3, then on Day 1 of every other subsequent cycles starting with Cycle 5 (eg, Cycles 5, 7, 9, etc), and then at the end of study treatment visit. After patients discontinuation from the active study treatment phase, FACT-B questionnaire will continue to be collected during the follow-up period every 6 months (+/- 7 days) from the last dose of investigational product until patient permanent discontinuation from study or end of follow-up period whichever occurs first. Completed questionnaires are always considered source document and must be filed accordingly.

Patients must complete these instruments in clinic (cannot be taken home) and prior to having any tests and to any discussion of their progress with healthcare personnel at the site. Interviewer administration in clinic may be used under special circumstances (eg, patient forgot their glasses or feels too ill). Completion of FACT-B during the follow-up period should also be completed by the patients during a scheduled clinic visit whenever possible. However, if no clinic visits are being scheduled during that time interviewer administration via phone call may be used instead and documented accordingly in the patient source notes.

7.4.1. EuroQol Health Utilities Index EQ-5D (Appendix 5)

The EuroQol-5D (EQ-5D) is a 6 item instrument designed to assess health status in terms of a single index value or utility score. It consists of 5 descriptors of current health state (mobility, self care, usual activities, pain/discomfort, and anxiety/depression); a patient is asked to rate each state on a three level scale (1=no problem, 2=some problem, and 3=extreme problem) with higher levels indicating greater severity/impairment. It also includes a visual analogue scale: the EQ VAS. The EQ VAS records the patient's self rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction and 1 as perfect health.

7.4.2. Functional Assessment of Cancer Therapy-Breast (FACT-B) [Version 4] (Appendix 6)

The Functional Assessment of Cancer Therapy (FACT) is a modular approach to assess patient health-related quality of life using a 'core' set of questions (FACT-G) as well as a cancer site-specific module.

The FACT-G is a 27-item compilation of general questions divided into 4 domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being.

The FACT-B consists of the FACT-G (27-items) and a breast-specific module: a 10-item instrument designed to assess patient concerns relating to breast cancer. Patients are asked to respond to a likert scale where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much.

7.5. Biomarker Assessment

Tumor tissues are required from all patients for study participation.

Retrospective confirmatory testing of tumor tissue samples for ER status will be performed in a central laboratory designated by the sponsor using a validated test. Results from this testing will be used for sensitivity analyses and will not be made available to the sites. In addition, tumor tissue biomarkers, including DNA, RNA and protein analytes, will be analyzed to investigate possible associations with resistance/sensitivity to treatment with study drugs. Biomarkers that will be analyzed will be selected based on their known relevance to mechanisms involved in cell cycle regulation. Examples of such biomarkers include CCND1 and CDKN2A gene copy number, cdk4 and cdk6 RNA expression, and Ki67, pRb and p16 protein expression.

Submission of formalin-fixed paraffin embedded (FFPE) tumor samples (blocks) of adequate size to allow for three 0.6 mm diameter x 5 mm deep cores that will be used to generate a tissue microarray are needed. If FFPE tissue block cannot be provided, a minimum of 12 glass slides each containing an unstained 5-micron FFPE tissue section, will be required for patient participation.

Tissue sample from a metastatic or recurrent tumor lesion must be provided whenever possible. If such tissue sample is unavailable, a *de novo* fresh biopsy is recommended when, in the investigator's judgment, such biopsy is feasible and can be safely performed. A sample of the original diagnostic tissue (ie, archival) will also be collected when available and sent to the sponsor-designated central laboratories for assessment of biomarkers associated with sensitivity and/or resistance to PD-0332991 (eg, Ki67, CDKN2A (p16), pRb). Retrospective confirmation of ER status and HER2 status when needing to be repeated for eligibility purpose will be performed using the most recent tumor sample. Original diagnostic tumor tissue will be used for confirmation of ER and HER-2 status in the event that a recurrent/metastatic tissue sample is not available and a fresh biopsy of the recurrent/metastatic lesion is not feasible.

Note: Tissue sample collected after neoadjuvant treatment is not acceptable for eligibility purposes as the molecular characteristics of the sample may be different from the original diagnostic tissue sample.

Tissue samples from all patients will be used for additional biomarker analyses. Detailed information about biomarker sample collection, preparation, storage, labeling, and shipment is indicated in the Study Reference Manual.

7.5.1. Optional Tumor Tissue Biopsy for Molecular Profiling

An optional fresh metastatic/recurrent tumor biopsy sample should be collected at the end of treatment visit for patients who discontinue treatment due to disease progression. The tumor tissue will be used to determine possible mechanisms of resistance to study treatment.

7.6. Retained Pharmacogenomic Sample(s)

7.6.1. Pharmacogenomics of Drug Response

Genomic and metabonomic variation may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomics. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting samples for pharmacogenomic analyses and retaining them in the Pfizer BioBank makes it possible to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study.

A single 4 mL blood sample (Prep D1; K₂ **edetic acid (ethylenediaminetetraacetic acid)** (EDTA) whole blood collection optimized for DNA analysis) will be collected pre-dose at the Cycle 1 Day 1 to be retained for potential pharmacogenomic analyses related to drug response or adverse drug reactions. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Retained Pharmacogenomic Sample(s) will be collected from all patients unless prohibited by local regulations. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

7.6.2. Additional Pharmacogenomic Research (Optional)

Unless prohibited by local regulations, patients will be asked to indicate on the consent form whether they will allow the Retained Pharmacogenomic Sample to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions.
- Samples may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics.

Patients need not provide additional samples for the uses described in [Section 7.6.1](#); the samples specified in [Section 7.6.1](#) will be used. Patients may still participate in the clinical trial if they elect not to allow their Retained Pharmacogenomic Samples to be used for the additional purposes described in [Section 7.6.2](#).

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. 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.

As part of ongoing safety reviews conducted by the sponsor, any non-serious adverse event 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.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least one dose of investigational product through the patient's last visit.

If a patient begins a new anti-cancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation 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 symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breast feeding;
- Medication error;
- Occupational exposure.

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

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- 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 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 reporting as an AE.

8.5. 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.

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 safety reporting 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 safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see Section on [Severity Assessment](#)).

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 subject 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.

8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on [Serious Adverse Event Reporting Requirements](#)).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤ 2 X ULN or not available.
- For patients with preexisting ALT or AST or total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
 - For patients with pre-existing AST **or** ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values and ≥ 3 X ULN, or ≥ 8 X ULN (whichever is smaller).

Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥ 3 times the upper limit of normal (whichever is smaller).

The patient should return to the investigational 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, and the possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of 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), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria

defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.6. 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 should be 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 work-up of persistent pre-treatment lab 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;

- Pre-planned 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 non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.7. Severity Assessment

As required on the AE CRFs, the investigator will report adverse events using concise medical terminology (verbatim) as well as collect on the CRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (version 4.0, Publish Date: May 28, 2009, <http://ctep.cancer.gov/reporting/ctc.html>) and will use the following definitions of severity to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 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.

8.8. 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 in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse 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 (see Section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

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In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. 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).

2. 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 study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on an SAE Report Form and Exposure in Utero (EIU) 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) using the EIU 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 EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU 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 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 serious adverse events when the investigator assesses the infant death as related or possibly related to the exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. 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 study 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.

8.10. 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 adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF); however, a copy of the completed SAE Report form is maintained in the investigator site file.

8.11. Withdrawal Due to Adverse Events (See Also Section on [Patient Withdrawal](#))

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

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or 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 or its designated representative.

8.13.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

In addition to recording observed or volunteered adverse events, certain additional data will be solicited from the patients in this study to more fully characterize the clinical pharmacology of PD-0332991/placebo in combination with letrozole. These additional measurements are contained under [Section 7.4](#) and include Patient Reported Outcomes.

Patient reported outcomes are collected and evaluated in a different manner than the observed or volunteered adverse events. Given these differences, no attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and the additional data collected from patients to more fully characterize the clinical pharmacology of PD-0332991/placebo in combination with letrozole. These additional data will be presented in separate tables, figures, and data listings, and will be reviewed in the final study report. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded on the Adverse Event pages on the Case Report Form (CRF).

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary purpose of this study is to demonstrate that the combination of PD-0332991 with letrozole is superior to placebo plus letrozole in prolonging PFS in postmenopausal women with ER (+), HER2 (-) ABC who have not received any prior systemic anti-cancer treatment for advanced disease. The study is designed to test the null hypothesis that the true PFS distributions for both PD-0332991 plus letrozole and placebo plus letrozole arms are the same with a median PFS 9 months versus the alternative hypothesis that the true PFS distribution has a median that is longer than 9 months⁴ for the PD-0332991 plus letrozole arm.

Under the original study design, 450 patients were to be enrolled using a 2:1 randomization schema. A total of 239 PFS events would be required to have 90% power to detect a hazard ratio of 0.64. On 03 January 2014, the protocol was amended to revise the study drug administration instructions from a recommended fasting state to administration with food and to prohibit the concomitant use of proton-pump inhibitors, as both conditions were found to negatively impact PD-0332991 plasma exposures. To mitigate the impact on efficacy results of potentially lower PD-0332991 exposures in some patients, an adjustment is now being made to the alternative hypothesis and an additional 200 patients will be enrolled into the study, and required number of PFS events for final analysis will be increased to 347. This will allow the trial to maintain a 90% power to detect significant treatment difference assuming a true hazard ratio of 0.69 in favor of the PD-0332991 plus letrozole arm using a one sided log rank test at a significance level of 0.025.

The sample size for this study is determined based on the assumptions that the median PFS for patients receiving placebo plus letrozole in the first-line treatment setting is 9 months and a risk reduction by 31% (hazard ratio of 0.69) or an improvement by 44% to median PFS of 13 months in the PD-0332991 plus letrozole treatment is clinically significant. A total of 347 events are required in the 2 arms of the study based on a 2:1 randomization to have 90% power to detect a difference assuming a true hazard ratio of 0.69 in favor of the PD-0332991 plus letrozole arm using a one-sided, log-rank test at a significance level of 0.025. Assuming a 15% drop-out rate on either treatment arm, a non-uniform accrual accomplished over a 15-month period and follow-up for about 10 months after the last patient is enrolled, a total sample size of approximately 650 patients (approximately 433 in the PD-0332991 plus letrozole arm and approximately 217 in the placebo plus letrozole arm) is required.

The sample size described above will also allow the assessment of differences in the secondary endpoint of overall survival (OS) with a high level of significance. The OS outcome of a reported Phase 3 clinical trial in a similar patient population demonstrated a median of 34 months for the arm receiving letrozole.⁴ Using this value as an assumption with a hypothesized 26% risk reduction (hazard ratio of 0.74) or 35% improvement in median OS (from 34 months to 46 months) in patients randomized to receive PD-0332991 plus letrozole and follow-up period of approximately 68 months, evaluation of 390 events using a one-sided log-rank test is required for a significance level of 0.025 and power of 80% to detect the difference.

9.2. Analysis Population

9.2.1. Intent-to-Treat Population (ITT)

The ITT population will include all patients who are randomized, with study drug assignment designated according to initial randomization. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

9.2.2. As-Treated Population (AT)

The AT population will include all patients who receive at least 1 dose of study treatment (ie, PD-0332991/placebo or letrozole/placebo), with treatment assignments designated according to actual study treatment received. The AT population will be the primary population for evaluating treatment administration/compliance and safety. Efficacy endpoints may be assessed in this population as well.

9.3. Efficacy Analysis

All efficacy analyses will be based on intent-to-treat (ITT) population. Some efficacy analyses will also be performed on the AT population. All analyses will be performed by using SAS[®] Version 9.1.3 or higher.

All primary and secondary endpoints based on radiological (and photographic where applicable) assessments of tumor burden (ie, PFS, OR, DR, DC) will be derived using the local radiologist's/investigator's assessment. Radiographic images and clinical information collected on-study will also be reviewed by a blinded independent third-party core imaging laboratory to verify investigator reported tumor assessments. This information will be used for supportive analyses.

9.3.1. Analysis of Primary Endpoint

The primary endpoint is PFS which is defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PFS data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die while on study. Patients lacking an evaluation of tumor response after randomization will have their PFS time censored on the date of randomization with a duration of 1 day. Additionally, patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumor assessment prior to the start of the new therapy.

The primary analyses of PFS will be performed in the ITT population. A stratified log-rank test (one-sided) will be used to compare PFS time between the 2 treatment arms at the interim and/or final analyses with the overall significance level preserved at 0.025 (one-sided). The stratification factor(s) are specified in [Section 3](#). PFS time associated with each treatment arm will be summarized for the ITT population using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles of the event-free time will be reported. The Cox Proportional hazards model will be fitted to compute the treatment hazard ratio and the corresponding 95% CI.

PFS will also be evaluated in the AT Population and the stratified long-rank test (one-sided, $\alpha=0.025$) will be used. In addition, to assess the impact of proton-pump inhibitors and fasting condition, PFS will also be evaluated in the population excluding patients who took proton-pump inhibitors and/or any other antacid medications concomitantly with study drug under fasting conditions during the active treatment phase.

9.3.2. Analysis of Secondary Endpoints

The secondary efficacy endpoints are:

Survival

Overall Survival (OS) is defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time will be censored to last date the patient is known to be alive.

All patients randomized will be considered evaluable for OS. OS will be hierarchically tested for significance at the time of PFS analyses, provided the primary endpoint, PFS, is statistically significant at the PFS interim or final analyses. A stratified log-rank test (using the same stratification factors as for the PFS analysis) will be used to compare OS between the treatment arms. OS for the two arms will be assessed using Kaplan-Meier methods and displayed graphically where appropriate. The median event times and 95% CIs will be estimated. Cox regression models will be used to estimate the treatment hazard ratio and its 95% confidence interval.

The 1-year survival probability will be estimated using the Kaplan-Meier method and a two sided 95% CI for the log [-log(1 year survival probability)] will be calculated using a normal approximation using the Greenwood's formula, and then back transformed to give a CI for the 1-year survival probability itself. The 2-year, and 3-year survival probabilities will be estimated similarly.

Objective Response (OR)

Objective response is defined as a complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1; [Appendix 7](#)) recorded from randomization until disease progression or death due to any cause.

A patient will be considered to have achieved an OR if the patient has a sustained complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the OR rate analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) on each randomized treatment arm will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients randomized to the respective treatment arm (“response rate”). A 95% CI for the response rates will be provided. Response rate comparisons between the 2 treatment arms as randomized will be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis.

Analyses for ORR will be performed on the ITT population based on the investigator’s assessment as well and also on the review of the blinded independent third-party core imaging laboratory.

In addition, the best overall response for each patient will be summarized by treatment arm.

Disease Control (DC)

Disease control (DC) is defined as complete response (CR), partial response (PR), or stable disease (SD) ≥ 24 weeks according to the RECIST version 1.1 ([Appendix 7](#)) recorded in the time period between randomization and disease progression or death to any cause.

The DC rate (DCR) on each randomized treatment arm will be estimated by dividing the number of patients with CR, PR, or SD ≥ 24 weeks by the number of patients randomized to the treatment arm. A 95% CI for the DC rates will be provided. DC rate comparison between the two treatment arms as randomized will be assessed using CMH test with the same stratification factors as for the PFS analysis.

Analyses for DCR will be performed on the ITT population based on the investigator’s assessment as well and also on the review of the blinded independent third-party core imaging laboratory.

Duration of Response (DR)

Duration of response (DR) is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. DR data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die due to any cause while on study.

DR will only be calculated for the subgroup of patients with an objective response.

DR for the two treatment arms will be summarized using Kaplan-Meier methods and displayed graphically, where appropriate. The median event time and 95% CI for the median will be provided for each endpoint.

All of these secondary analyses will be conducted at a one-sided 0.025 level of significance. Additional sensitivity analyses will be outlined in the SAP.

Additional secondary endpoints include:

Patient Reported Outcomes (PRO)

Breast cancer-specific quality of life scores and change from baseline scores will be compared between the treatment arms at various time points using a mixed model repeated measures (MMRM) approach adjusting for specified covariates. In addition, analyses will be performed to determine if the change from baseline scores achieve the appropriate minimally important difference (MID) cut-off for the scale being examined. Patients from the ITT population who completed a baseline assessment and at least one post-baseline assessment prior to study treatment discontinuation will be considered evaluable for the patient reported outcome analysis.

In addition to the above analyses, an examination of the time to deterioration (TTD) also will be carried out using survival analysis methods. A composite definition for deterioration based on death, tumor progression, and MID will be used.

Electrocardiogram (ECG) Analysis

QT measurements corrected by heart rate (QTc) will be used for the data analysis and interpretation. In addition to commonly used techniques including Bazett's (QTcB) and Fridericia's (QTcF) methods, a study-specific correction method will be evaluated (QTcS) for the ECG sub-group of Arm A. QTcF will be used for the primary analysis.

The QTc analysis will be based on a non-inferiority hypothesis testing framework. Approximately 40 PD-0332991 plus letrozole treated patients are needed to establish non-inferiority (no unacceptable QTc prolongation from the PD-0332991 plus letrozole combination) between post-dose baseline and baseline (Δ QTc) at all 5 QTc sampling time points on Cycle 1 Day 14 with 90% power. The test is based on a one-sided difference in means t-test for paired Δ QTc with significance level of 0.05. The difference in means between Δ QTc under the alternative hypothesis is 10 msec, assuming a non-inferiority margin of 20 msec and the standard deviation of the paired differences equals 16 msec (based on Study A5481003). If the upper bounds of one-sided 95% confidence intervals of Δ QTc for all 5 QTc sampling time points are below 20 msec, the post-baseline dose QTc interval is considered to be "non-inferior" to the baseline; the QTc effect of PD-0332991 in combination with letrozole is concluded to not be unacceptable.

Since this is a double-blind study with a 2:1 randomization, approximately 60 patients will be needed for QTc evaluation to ensure approximately 40 patients from the experimental arm (ie, PD-0332991 plus letrozole).

Changes in QTc (QTcB, QTcF, and/or QTcS) from baseline will be summarized using descriptive statistics and categorical analysis by nominal time point. A random effect model with the nominal time point as a fixed effect and the patients as a random effect will be used to estimate the mean change in QTc (QTcF, QTcS optional) from baseline at each post-baseline nominal time point. The 90% confidence intervals for the changes from baseline in QTc will be provided at each post-baseline nominal time point.

Pharmacokinetic/Pharmacodynamic Analysis of QTc

Concentration data of PD-0332991 will be listed by patient and by actual collection time and day.

Concentration-QTc analysis will be conducted using the PK and ECG data from this study. Linear, log-linear, and/or saturable models will be examined for the concentration-QTc relationship. Exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model. Diagnostic evaluation will be included to explore the adequacy of the model. Refer to SAP for details of the analysis. The results of these modeling analyses may be reported separately from the clinical study report.

Pharmacokinetic Analysis

Average trough concentrations will be listed by patient. Summary statistics will be provided for trough concentrations by study cycle and for average trough concentrations by patient. The relationship between trough concentration and potential covariates will be evaluated. All patients treated with PD-0332991 and for whom drug plasma concentration results (from at least 1 visit) are available will be included in the analysis.

Exposure/Response Analysis

In addition, the relationship between exposure and efficacy and safety endpoints will be explored, as necessary, based on emerging efficacy and safety data. Refer to SAP for details of the analyses. The results of these modeling analyses may be reported separately from the clinical study report.

Biomarker Analysis

For baseline continuous endpoint data, descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided by treatment arm.

For baseline categorical data, the number and percentage of patients in each category will be provided by treatment arm.

Appropriate statistical methods may be used to investigate any possible relationship of biomarker levels with PD-0332991 plus letrozole anti-tumor efficacy.

9.4. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate.

9.5. Safety Analysis

The AT population will be the primary population for safety evaluation. Summaries of AEs and other safety parameters will be provided as appropriate.

Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible (<http://ctep.info.nih.gov/reporting/ctc.html>).

Adverse events will be summarized by treatment and by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. Adverse events will be graded by worst NCI CTCAE v4.0 Grade. Adverse events will be summarized by cycle and by relatedness to trial treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v4.0 Grade 3 or higher, trial drug-related events, and serious adverse events will be considered with special attention.

Laboratory Abnormalities

Hematology and chemistry laboratory data will be summarized by treatment and by cycle. The laboratory results will be graded according to the NCI CTCAE v4.0 severity grade. The frequencies of the worst severity grade observed will be displayed by study treatment. Shift tables will be provided to examine the distribution of laboratory toxicities. For parameters for which an NCI CTCAE v4.0 scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment.

Ocular Events

Ocular events will be reported as part of the adverse event analysis described above. Additionally, changes in lens grading while on study treatment will be analyzed as described in the Statistical Analysis Plan.

Summary and Categorical Electrocardiogram (ECG) Analysis

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

For all patients in the safety analysis population, individual change in QTc (QTcF, QTcB, QTc S) will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

For all patients in the safety analysis population, categorical analysis of the QTcF/QTcB/QTcS data will be conducted and summarized as follows:

1. The number and percentage of patients with maximum increase from baseline in QTcF/QTcB/QTcS (<30, 30- 60, and \geq 60 msec).
2. The number of and percentage patients with maximum post-dose QTcF/QTcB/QTcS (<450, 450-<480, 480- <500, and >500 msec).
3. PR changes from baseline \geq 50% if absolute baseline value was <200 msec, and \geq 25% if absolute baseline value was >200 msec.
4. QRS changes from baseline \geq 50% if absolute baseline value was <100 msec, and \geq 25% if absolute baseline value was >100 msec.

The analyses described above for all patients will be repeated separately for the ECG sub-population in group 1 for QTcF/QTcB/QTcS.

9.6. Interim Analysis

The study is designed to have one interim analysis and the final analysis based on the primary PFS endpoint. A formal efficacy boundary (Haybittle-Peto) for rejecting the null hypothesis will be used for the interim analysis. To protect the integrity of the study and to preserve the type-1 error rate, a fraction of alpha (0.000013) for efficacy will be spent at the interim analysis and accounted for in the overall type I error rate. The overall significance level for the efficacy analysis of PFS will be preserved at 0.025 (1-sided test).

The purposes of the interim analysis are to allow early stopping of the study for futility and efficacy, to assess safety of the combination regimen, and to potentially adjust the sample size. The interim analysis will be performed after approximately 226 patients have documented progressive disease or die (approximately 65% of the total events expected). If the value of the test-statistic exceeds the Haybittle-Peto efficacy boundary ($z \geq 4.2059$, $p \leq 0.000013$) the trial may be stopped for efficacy. Under exponential distribution assumption, this boundary equates to a hazard ratio of ~ 0.55 or smaller in favor of the palbociclib plus letrozole arm versus the letrozole alone arm. Alternatively, as appropriate, the sample size of the study may be adjusted using the method outlined by Cui et al.⁷⁵ If the results of the interim analysis indicate serious safety concerns, the sponsor will communicate with the Health Authorities regarding stopping the clinical trial.

An interim analysis of efficacy is also planned for the secondary OS endpoint. The analysis will be performed at the time of the interim or final PFS analyses if the primary analysis for PFS is positive. The nominal significance levels for the interim and final analyses of OS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule.

The overall significance level for the efficacy analysis of OS will be preserved at 0.025 (one-sided test). Details of the analysis will be provided in the SAP.

OS will be hierarchically tested for significance at the time of PFS analyses, provided the primary endpoint, PFS, is statistically significant at the interim and/or final PFS analyses. If OS does not yield a significant result at these analyses, OS will be tested at the final OS analysis. If PFS is not significant at the interim and/or final PFS analyses, OS will not be statistically evaluated.

9.7. Data Monitoring Committees

The study will use an External Data Monitoring Committee (E-DMC). The E-DMC membership and governance is outlined in a separate charter.

The E-DMC will be responsible for ongoing monitoring of the efficacy and safety data from patients in the study according to the Charter. The E-DMC will make recommendation as to whether or not the trial should continue based on ongoing reviews of safety data. In addition, the E-DMC will also evaluate interim efficacy data and make a recommendation regarding study continuation based on observed results of the study. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate. The sponsor will designate a biostatistician not affiliated with the project to prepare data for E-DMC review. Only if action or consultation with Health Authorities is required will other sponsor staff be involved. Clinical sites will be restricted from access to study results until the conclusion of the study.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agents 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 is 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 study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), 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 study site for the inspection and will allow Pfizer or its agent,

whenever feasible, to be present during the inspection. 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 is true. Any corrections to entries made in the CRFs, 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's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer or its designated agents, 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, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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 (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on harmonization guideline for GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

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

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC, and available for inspection.

The investigator must ensure that each study patient, or his/her legal representative, 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 or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document. The patient will be provided with a copy of the signed informed consent form(s).

12.4. Patient Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. 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 Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Patient Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PD-0332991 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a week of notification. 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 this study 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 for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

[EudraCT](#)

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report 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 principal investigator of the results of the study based on information collected or generated by principal investigator, 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 they are 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 multi-centre study, Investigators agree that the first publication is to be a joint publication covering all study sites and that any subsequent publications by the principal investigator 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, Investigators are free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institutions 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 Clinical Study Agreement between Pfizer and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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 subjects, and the CSA will control as to all other issues.

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Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

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Appendix 2. Sponsor Approved HER2 Assays

HER2 results based on 1 of the following commercial kit assays are acceptable (for the purposes of study entry)

IHC Approved Assay	FISH Approved Assay	CISH Approved Assay	Other Approved Assay
HercepTest™	Pathvysion HER2 DNA Probe Kit	SPOT-Light® HER2 CISH™ Kit	INFORM HER2 Dual ISH DNA Probe Cocktail Assay
PATHWAY™ Her2 ^a	INFORM HER2/neu Probe Kit	HER2 CISH PharmDx™ Kit	-
Bond™ Oracle™ HER2 IHC System	HER2 FISH PharmDx™ Kit	-	-
PATHWAY HER-2/neu ^b	-	-	-

Footnote:

- a. PATHWAY™ Her2 (clone CB11) is a mouse monoclonal antibody intended for laboratory use for the semi-quantitative detection of c-erbB-2 antigen in sections of formalin fixed, paraffin embedded normal and neoplastic tissue on a Ventana automated immunohistochemistry slide staining device.
- b. PATHWAY HER-2/neu (clone 4B5) is rabbit monoclonal antibody intended for the semi-quantitative detection of HER2 antigen in sections of formalin-fixed, paraffin-embedded normal and neoplastic tissue. Created to run on a Ventana automated immunohistochemistry slide staining device, it is indicated as an aid in the assessment of breast cancer patients for whom Herceptin treatment is considered.

Appendix 3. List of Drugs Known to Predispose to Torsade de Pointes

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

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

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: <http://www.crediblemeds.org/>. This list is not meant to be considered all inclusive. See website for current list.

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Appendix 4. Bone Marrow Reserve in Adult

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	13.1	13.1
	Cranium	165.8	0.75	124.3		
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle :			86.7	8.3	8.3
	2 Humerus, head & neck	26.5	0.75	20.0		
	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	7.9	10.2
	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		
	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	36.2
	2 os coxae	310.6	0.75	233.0	22.3	
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		3.8

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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	3.4	28.4
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1		
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9	14.1	
	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		
	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	10.9		
1 pair	27.8	All 0.75	20.8			
2	29.1		21.8			
3	31.8		23.8			
4	32.1		24.1			
5	31.4		23.6			
TOTAL		1497.7		1045.7	100.0	100.0

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Appendix 5. EuroQol Health Utilities Index EQ-5D



Health Questionnaire

*English version for the UK
(validated for Ireland)*

SAMPLE

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By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**



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Appendix 6. Functional Assessment of Cancer Therapy-Breast (FACT-B) [Version 4]

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
011	I have been short of breath.....	0	1	2	3	4
012	I am self-conscious about the way I dress.....	0	1	2	3	4
013	One or both of my arms are swollen or tender.....	0	1	2	3	4
014	I feel sexually attractive	0	1	2	3	4
015	I am bothered by hair loss	0	1	2	3	4
016	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
017	I worry about the effect of stress on my illness	0	1	2	3	4
018	I am bothered by a change in weight	0	1	2	3	4
019	I am able to feel like a woman	0	1	2	3	4
020	I have certain parts of my body where I experience pain....	0	1	2	3	4

Appendix 7. 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 LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical examination 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 subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

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

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

Recording Tumor Assessments

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

Target lesions

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

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

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

Non-target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective 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 (eg, poorly visible unless due to being too small to measure),
 - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

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

New Lesions

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

Supplemental Investigations

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

Subjective progression

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

Table 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

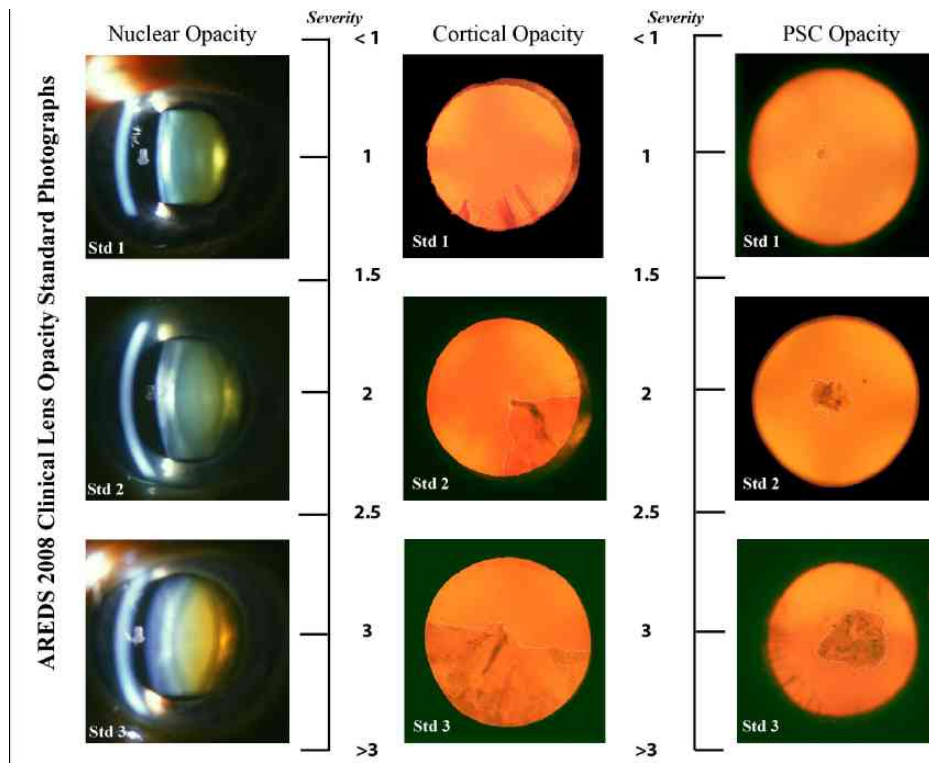
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If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

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

Appendix 8. Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedure

- Dilate pupils to at least 5 mm diameter.
- Use slit lamp with ~10X magnification.
- Use brightest beam intensity.
- Nuclear opacity.
 - Orient beam at 45° to viewing axis.
 - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width.
 - Compare opalescence of nucleus with that in standard photos.
- Cortical and PSC opacities.
 - Select wide slit beam setting optimum for retro-illumination of lens.
 - Visualize lens opacities against red fundus reflex background.
 - Count only opacities definitely visible against red reflex.
 - Mentally combine all cortical opacities into one contiguous area.
 - Compare total opacity area with that in standard photos.
- Classify each opacity with scale defined by 3 standard photos.
- Select nearest half-step.
 - Similar to standard or between two standards.
 - Obviously less than mildest standard or greater than most severe.



Appendix 9. List of Abbreviation

ABC	Advanced Breast Cancer
ASCO	American Society of Clinical Oncology
AE	Adverse Event
ALT	Alanine Aminotransferase
AI	Aromatase Inhibitor
ANC	Absolute Neutrophil Count
ANSM	Agence Nationale de Sécurité du Médicament
AREDS	Age-Related Eye Disease Study
AST	Aspartate Aminotransferase
AT	As Treated
AUC	Area Under the Curve
BC	Breast Cancer
BUN	Blood Urea Nitrogen
CAP	Chest, Abdomen, Pelvis OR College of American Pathologists depending on context.
CCND1	Cyclin D1
CDK	Cyclin-Dependent Kinase
CDKN2A, p16 ^{Ink4A}	Cyclin-Dependent Kinase Inhibitor 2A
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridization
CLIA	Clinical Laboratory Improvement Amendments
C _{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSA	Clinical Study Agreement
CSF	Colony-Stimulating Factors
CT	Computed Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
DC	Disease Control
DCR	Disease Control Rate
DFI	Disease Free Interval
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	External Data Monitoring Committee
EDTA	Ethylenediaminetetraacetic acid

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EIU	Exposure In Utero
EQ-5D	Dimension Health State EuroQoL Score
ER	Estrogen Receptor
FACT	Functional Assessment of Cancer Therapy
FACT-B	Functional Assessment of Cancer Therapy - Breast
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	US Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FIH	First in Human
FISH	Fluorescent In Situ hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Hb	Hemoglobin
HDPE	High Density Polyethylene
HER	Human Epidermal Growth Factor Receptor
hERG	Human Ether-à-Go-Go
HR	Heart Rate
IB	Investigator's Brochure
IC ₅₀	Concentration of 50% Inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
IOP	Intraocular Pressure
IMPAKT	Improving Care and Knowledge through Translational Research
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ISH	In Situ Hybridization
ITT	Intent-to-Treat
LFT	Liver Function Test
LPD	Local Product Document
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PCD	Primary Outcome Completion Date

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PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response or Progesterone Receptor (depending on context)
PR	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex.
PS	Performance Status
PSC	Posterior Subcapsular Cataract
PRO	Patient Reported Outcome
PT	Prothrombin Time
QD	Quaque Die (once daily)
QRS	The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram. The QRS complex reflects the rapid depolarization of the right and left ventricles.
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QT _c	QT interval corrected for heart rate
QT _{cB}	QT interval corrected for heart rate using Bazett's formula
QT _{cF}	QT interval corrected for heart rate using Fridericia's formula
RANKL	Receptor Activator of Nuclear Factor Kappa B Ligand
RB/Rb	Retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	The interval between an R wave and the next R wave
R _{ac}	Accumulation Ratio
SAE	Serious Adverse Event
SD	Stable Disease or Standard Deviation (depending on context)
SPC	Summary of Product Characteristic
t _½	Terminal Elimination Half-life
TdP	Torsade de Pointes
T _{max}	Time for C _{max}
UK	United Kingdom
ULN	Upper Limit of Normal
USPI	United States Package Insert
V _z /F	Apparent Volume of Distribution
WBC	White Blood Cell