Protocol GEICAM/2013-02
Phase III study of Palbociclib (PD-0332991) in combination with Endocrine therapy (exemestane or fulvestrant) versus chemotherapy (capecitabine) in Hormonal Receptor (HR) positive/HER2 negative Metastatic Breast Cancer (MBC) patients with Resistance to Aromatase inhibitors
"The PEARL study"

Sponsor: GEICAM (Spanish Breast Cancer Research Group Foundation)

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Sponsor Study Code: **GEICAM/2013-02**

EudraCT Number: 2013-003170-27

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SUMMARY OF THE STUDY PROTOCOL

Study Title: Phase III study of Palbociclib (PD-0332991) in combination with Endocrine therapy (exemestane or fulvestrant) versus chemotherapy (capecitabine) in Hormonal Receptor (HR) positive/HER2 negative Metastatic Breast Cancer (MBC) patients with Resistance to Aromatase inhibitors. "The PEARL study"

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Sponsor: GEICAM (Spanish Breast Cancer Research Group Foundation)

Countries: Austria, Hungary, Israel and Spain.

Study Rationale:

Endocrine therapy is the cornerstone treatment for patients with hormone-receptor (HR)–positive, HER2 negative breast cancer. In postmenopausal patients, aromatase inhibitors (e.g., letrozole and anastrozole) have become the treatment of choice. Unfortunately, not all patients respond to endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance).

On early disease recurrence/progression, the treatment options include other classes of aromatase inhibitors, estrogen-receptor (ER) antagonists/degrader or chemotherapy; being chemotherapy the most accepted one for the resistant patients. Within the chemotherapy regimens, capecitabine seems one of the best options.

The research focusing on resistance to endocrine therapies in HR-positive breast cancer has aimed to identify new therapeutic strategies that would enhance the efficacy of endocrine therapies.

Published preclinical data suggest that estrogen receptor positive (ER-positive) /HER2 negative breast cancers are dependent on cyclin-dependent kinases 4/6 (CDK4/6) function and that inhibition of this target may be an effective translational therapeutic strategy. The Pfizer compound, palbociclib, is an oral novel CDK4/6 inhibitor that seems to be synergistic with anti-hormonal therapy in preclinical and clinical studies. Results from a randomized phase II study of letrozole vs letrozole plus palbociclib (PALOMA-1) confirmed the safety and tolerability of the combination and demonstrated an exciting efficacy with a hazard ratio for progression-free survival of 0.488 (95% CI 0.319–0.748; one-sided p=0.0004), with a median PFS increase from 10.2 to 20.2 months. The most common adverse event from the drug has been asymptomatic leucopenia which is an "on-target" effect. Although the study was not designed to perform a formal hypothesis testing for overall survival (OS) analysis due to the small sample size, it was

performed recently. It showed that the median OS was numerically longer in the palbociclib plus letrozole arm than in the letrozole alone arm, but results were not statistically significant (37.5 months vs 34.5 months; hazard ratio for death was 0.897 [95% CI:0.623, 1.294]; p = 0.281).

Based on these results, an international, randomized Phase III study comparing letrozole to letrozole + palbociclib as first-line treatment for ER-positive metastatic breast cancer (PALOMA-2) was also performed, which results are already available. PALOMA-2 included 666 postmenopausal patients with no prior systemic therapy for advanced breast cancer that were randomised 2:1 to receive palbociclib (oral 125 mg/day; 3 weeks on/1 week off) + letrozole (2.5 mg/day continuously) or placebo + letrozole every 28 days until disease progression, consent withdrawal or death. Patients were stratified by disease site, disease-free interval from end of (neo) adjuvant therapy, and prior hormone therapy (yes/no). The primary endpoint was investigator-assessed PFS, and the secondary endpoints included: overall survival, objective response rate, clinical benefit rate (CR + PR + SD ≥24 weeks), patient-reported outcomes, pharmacokinetics and safety. Baseline characteristics were well balanced between both treatment groups. The primary analysis showed a median PFS of 24.8 months (95% confidence interval [CI], 22.1 to not estimable) in the palbociclib-letrozole group, as compared with 14.5 months (95% CI, 12.9 to 17.1) in the placebo-letrozole group (hazard ratio for disease progression or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001). ORR was improved with palbociclib + letrozole (42.1% vs. 34.7%, p=0.031; 55.3% vs. 44.4% in patients with measurable disease [p=0.013]). CBR was 84.9% vs. 70.3% (p<0.0001). The most common grade 3 or 4 adverse events were neutropenia (occurring in 66.4% of the patients in the palbociclib-letrozole group vs. 1.4% in the placebo-letrozole group), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%), and fatigue (1.8% vs. 0.5%). Febrile neutropenia was reported in 1.8% of patients in the palbociclib-letrozole group and in none of the patients in the placebo-letrozole group. Permanent discontinuation of any study treatment as a result of adverse events occurred in 43 patients (9.7%) in the palbociclib-letrozole group and in 13 patients (5.9%) in the placebo-letrozole group. At the time of this primary analysis, the percentage of PFS events was less than 50% (43.7%) in the palbociclib plus letrozole arm. Due to that an updated analysis of PFS based on the investigator assessment was recently performed when the PFS event rate reached approximately 60% for the entire study population (55% in the palbociclib plus letrozole arm), which data confirmed the benefit for the addition of palbociclib to letrozole. The updated median PFS was 27.6 months (95% CI: 22.4, 30.3) in the palbociclib plus letrozole arm and 14.5 months (95% CI: 12.3, 17.1) for placebo plus letrozole. The observed hazard ratio for disease progression or death was 0.563 (95% CI: 0.461, 0.687; stratified 1-sided p<0.000001) in favor of palbociclib plus letrozole treatment. OS data was immature in both analysis and the final OS information is still pending.

In addition, a randomized, double blinded placebo control, global phase III study was completed to evaluate the efficacy of palbociclib + fulvestrant vs fulvestrant + placebo (+/- Goserelin depending of menopausal status) in HR-positive/HER2-negative breast cancer patients whose disease has progressed on endocrine therapy either during or within 12 months of completion of adjuvant endocrine therapy or while receiving or within 1 month of endocrine therapy for

advanced disease (PALOMA-3 study). The primary end point was investigator-assessed progression-free survival. A pre-planned interim analysis was performed by an independent data and safety monitoring committee after 195 events of disease progression or death had occurred. The median progression-free survival was 9.2 months (95% confidence interval [CI], 7.5 to not estimable) with palbociclib‑fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo‑fulvestrant (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001).

The most common grade 3 or 4 adverse events (AEs) in the palbociclib + fulvestrant group were neutropenia (62.0%, vs. 0.6% in the placebo + fulvestrant group), leukopenia (25.2% vs. 0.6%), anaemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Febrile neutropenia was reported in 0.6% of palbociclib-treated patients and 0.6% of placebo-treated patients. The rate of discontinuation due to AEs was 2.6% with palbociclib and 1.7% with placebo.

Additionally, the results of a prespecified analysis of OS in the PALOMA-3 study showed that the median OS was 34.9 months (95% CI, 28.8 to 40.0) in the palbociclib + fulvestrant group and 28.0 months (95% CI, 23.6 to 34.6) in the placebo + fulvestrant group (HR for death, 0.81; 95% CI, 0.64 to 1.03; P = 0.09; absolute difference, 6.9 months). CDK4/6 inhibitor treatment after the completion of the trial regimen occurred in 16% of the patients in the placebo–fulvestrant group. Among 410 patients with sensitivity to previous ET, the median OS was 39.7 months (95% CI, 34.8 to 45.7) in the palbociclib + fulvestrant group and 29.7 months (95% CI, 23.8 to 37.9) in the placebo + fulvestrant group (HR, 0.72; 95% CI, 0.55 to 0.94; absolute difference, 10.0 months). The median duration of subsequent therapy was similar in the two groups, and the median time to the receipt of CT was 17.6 months in the palbociclib + fulvestrant group, as compared with 8.8 months in the placebo + fulvestrant group (HR, 0.58; 95% CI, 0.47 to 0.73; P<0.001). No new safety signals were observed with 44.8 months of follow-up.

The PFS curve of PALOMA-1 and PALOMA-3 studies, however, seems to indicate that the effect of the drug on PFS was mainly due to the prevention of early progressions. In the first 4 months of the PALOMA-1 trial (AI sensitive patients), 40% of the patients in the letrozole arm had progressed vs only 20% in the letrozole + palbociclib arm; in the first 2 months of the PALOMA-3 trial (endocrine resistant patients), 37% of the patients in the fulvestrant arm had progressed vs only 20% in the fulvestrant + palbociclib arm. Those curves suggest that the main effect of palbociclib is the reversal of resistance to the anti-hormonal treatment.

A similar effect in that population of patients has been shown with the addition of the mTOR inhibitor everolimus to exemestane. The PFS with the combination of exemestane plus everolimus was 6.9 vs 2.8 months with exemestane alone. The combination of exemestane plus everolimus, however, produces significant toxicity.

Taking all this into consideration, the combination of anti-hormonal therapy with CDK4/6 inhibitors such as palbociclib may play an important role in HR-positive patients that have become resistant to hormones and should be compared to the standard of care in patients with

hormone-resistant HR-positive tumors, i.e. cytotoxic chemotherapy.

The initially proposed Phase III study was designed to provide the opportunity to confirm the clinical benefit of palbociclib in combination with exemestane. The study was designed to demonstrate that this combination provides superior clinical benefit compared to capecitabine in postmenopausal women with HR+/HER2- metastatic breast cancer who are resistant to non-steroidal aromatase inhibitors.

Emerging data suggest that the choice of endocrine partner with palbociclib is particularly important to create optimal synergy in endocrine resistance setting. Studies of resistance to hormonal therapies and ER biology have highlighted the important role of ER receptor degraders for sequential endocrine treatment after patients progressed on aromatase inhibitors (AIs). Recent studies revealed that the acquisition of *ESR1* mutations is a major mechanism of resistance to AIs. *ESR1* mutations were found to be associated with exposure to AIs during the adjuvant and metastatic settings. Patients with *ESR1* mutations had a substantially shorter PFS on subsequent AI-based therapy. In addition, the high incidence rate of *ESR1* mutation has been reported among patients who have been treated with AIs in MBC patients (BOLERO-2, PALOMA-3). More recently, data from PALOMA-3 and other studies suggest that fulvestrant may be active among patients whose tumors had *ESR1* mutation, while exemestane may be inactive. Thus among patients who have progressed on AIs, fulvestrant may be a better endocrine partner for palbociclib.

The present design provides the opportunity to confirm the clinical benefit of palbociclib in combination with endocrine therapy in relation to *ESR1* mutational status. The primary study objectives are to demonstrate that: 1) fulvestrant plus palbociclib provides superior clinical benefit compared to capecitabine in postmenopausal women with HR+/HER2- metastatic breast cancer who are resistant to aromatase inhibitors and that 2) endocrine therapy (fulvestrant or exemestane) in combination with palbociclib provides superior clinical benefit compared to capecitabine in postmenopausal women with HR+/HER2- metastatic breast cancer and whose tumor had estrogen receptor *(ESR1*) mutational status as wild type at study entry.

Study Design and Treatment:

This is an international, multicenter, open label, controlled, randomized phase III study comparing the efficacy and safety of palbociclib in combination with endocrine therapy (exemestane or fulvestrant) versus capecitabine in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to previous aromatase inhibitors (AI: exenestane, letrozole or anastrozole), defined as recurrence while on or within 12 months after the end of adjuvant treatment or progression while on or within 1 month after the end of treatment for advanced disease. It is not mandatory to have exemestane, letrozole or anastrozole as the most recent treatment before randomization but recurrence or progression while receiving or after the end of (in the metastatic setting *immediately* after the end of) the most recent systemic therapy

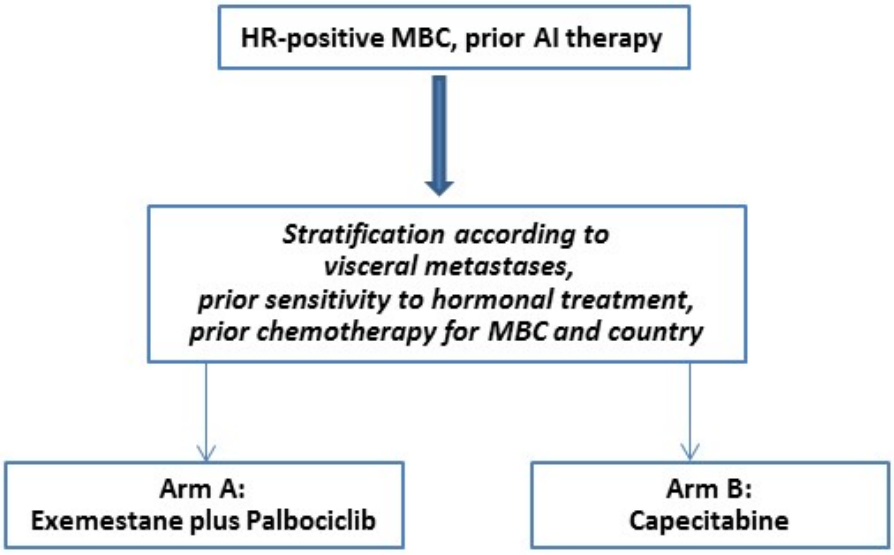
had to be documented before randomization. Patients must have measurable disease or at least one bone lesion, lytic or mixed (lytic + blastic), which has not been previously irradiated and is assessable by CT/MRI in the absence of measurable disease.

Approximately 300 patients were to be randomized 1:1 between the experimental arm (Arm A: 150 patients treated with palbociclib plus exemestane) and the control arm (Arm B: 150 patients treated with capecitabine) before the approval of the protocol version 5.0 dated 09Mar2016. (Cohort 1).

Approximately 300 additional patients will be randomized 1:1 between the experimental arm (Arm A: approximately 150 patients treated with palbociclib plus fulvestrant) and the control arm (Arm B: approximately 150 patients treated with capecitabine) from the approval of the protocol version 5.0 dated 09Mar2016 (Cohort 2).

Study Design:

Cohort 1



Patients will be stratified by site of disease (visceral vs non-visceral), by the prior sensitivity to hormonal treatment (yes vs no), by prior chemotherapy for MBC (yes vs no) and by country.

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

- ✓ Palbociclib, 125 mg, orally once daily on Day 1 to Day 21 followed by 7 days off treatment given as every 28 days cycles;

in combination with

- ✓ Exemestane, 25 mg, orally once daily (continuously).

In patients within the Pharmacokinetic (PK) sub-study, exemestane will be administered daily

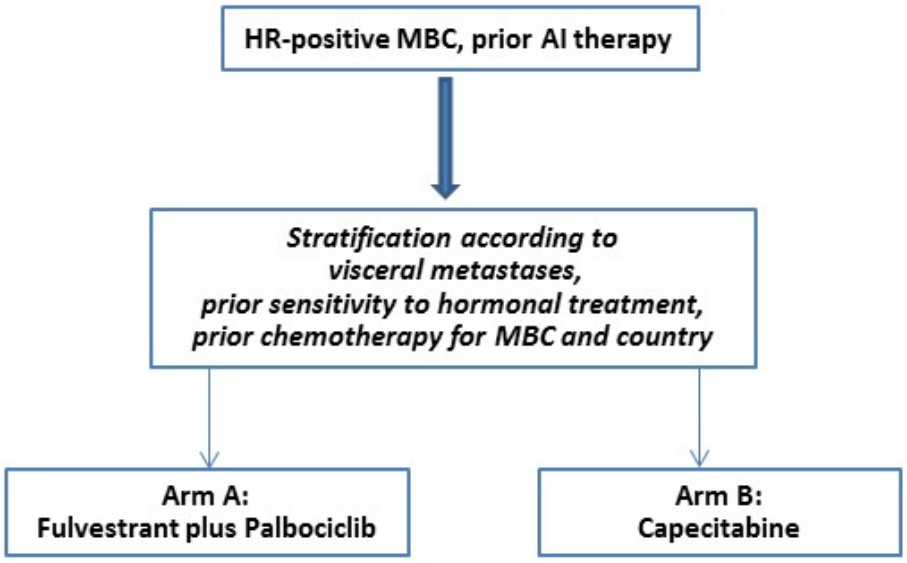
during a 7-day lead-in period (day minus-7 through day minus-1) immediately preceding cycle 1.

NOTE: The start date of each cycle will be given by the start date of palbociclib intake.

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

- ✓ Capecitabine, 1,250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000 mg/m^2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.

Cohort 2



Patients will be stratified by site of disease (visceral vs non-visceral), by the prior sensitivity to hormonal treatment (yes vs no), by prior chemotherapy for MBC (yes vs no) and by country.

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

- ✓ Palbociclib, 125 mg, orally once daily on Day 1 to Day 21 followed by 7 days off treatment given as every 28 days cycles;

in combination with

- ✓ Fulvestrant 500 mg, two 5ml intramuscular injections (one in each buttock) on Days 1 and 15 (±3 days) of Cycle 1, and then on Day 1 of each subsequent 28 days Cycle (± 3 days).

NOTE: The start date of each cycle will be given by the date of administration of fulvestrant.

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

- ✓ Capecitabine, 1,250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period,

given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000 mg/m^2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.

In both Cohorts patients will continue to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurs first. Patients with permanent discontinuation of palbociclib for a reason different than progression (i.e., toxicity due to palbociclib) will continue with exemestane/fulvestrant (in the active treatment phase) until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first. Patients with permanent discontinuation of exemestane/fulvestrant will be discontinued from the active treatment phase and entered into the follow-up phase.

Primary Objectives:

- To demonstrate that palbociclib in combination with fulvestrant is superior to capecitabine in prolonging Progression-Free Survival (PFS) in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors, regardless of the *ESR1* mutational status.
- To demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging PFS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors and whose tumor had estrogen receptor (*ESR1*) mutational status as wild type at study entry. *ESR1* mutational status will be determined by circulating free DNA (cDNA) and will be prospectively determined before the interims or final analyses. Patient tumor *ESR1* mutational status will be blinded to patients, investigators and study team.

Primary Endpoint:

- Progression-Free Survival (PFS) based on the investigator's assessment according to the RECIST version 1.1.

Secondary Objectives:

- To demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging PFS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors regardless of *ESR1* mutational status at study entry.
- To demonstrate that palbociclib in combination with fulvestrant is superior to capecitabine in prolonging Overall Survival (OS) in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors.
- To demonstrate that palbociclib in combination with endocrine therapy (exemestane or

fulvestrant) is superior to capecitabine in prolonging OS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors and whose tumor had estrogen receptor (*ESR1*) mutational status as wild type at study entry.

- To demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging OS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors regardless of *ESR1* mutational status at study entry.
- To compare other efficacy measures between the treatment arms: Objective Response Rate (ORR), Clinical Benefit Rate (CBR) and Response Duration (RD).
- To compare safety and tolerability between the treatment arms.
- To compare health-related quality of life between the treatment arms.
- To evaluate the Pharmacokinetics (PK) of the combination of exemestane with palbociclib (in selected sites and only in patients accepting to participate).

Secondary Endpoints:

- The following efficacy endpoints will be measured:
  - Overall Survival (OS).
  - Objective Response (OR): Complete Response (CR) plus Partial Response (PR) based on the investigator's assessment according to the RECIST version 1.1 in patients randomized with measurable disease.
  - Clinical Benefit (CB): CR plus PR plus stable disease based on the investigator's assessment lasting more than 24 weeks according to the RECIST version 1.1 in all randomized patients (ITT population).
  - Response Duration (RD) based on the investigator's assessment according to the RECIST version 1.1.
- Safety will be assessed by standard clinical and laboratory tests (hematology, serum chemistry). Adverse events grade will be defined by the NCI CTCAE v4.0.
- The PK will determine whether palbociclib influences the pharmacology of exemestane. Blood samples will be taken at the time defined in the protocol in patients included in the experimental arm of Cohort 1 (palbociclib plus exemestane) in selected sites. Enrollment of these patients were to be finalised at the completion of cohort 1 recruitment, samples from approximately 20 PK-evaluable patients were to be collected. .
- EORTC QLQ-C30, QLQ-BR23 and EQ-5D questionnaires.

Exploratory Objectives:

- To prospectively evaluate whether the magnitude of PFS and OS prolongation of palbociclib in combination with fulvestrant is the same in patients with *ESR1* mutational status as wild type and patients with *ESR1* mutational status positive at study entry.
- To prospectively evaluate whether PFS and OS of palbociclib in combination exemestane is better among those patients with *ESR1* mutational status as wild type than those patients with *ESR1* mutational status positive at study entry.
- To prospectively evaluate PFS and OS of capecitabine by *ESR1* mutational status.
- To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle (e.g, CCND1 amplification, CDKN2A deletion), drug targets (e.g. CDK 4/6), tumor sensitivity and/or resistance (e.g. Ki67, pRb, PIK3CA mutation, CCNE1 expression) or breast cancer (e.g. PTEN, *ERBB2, BRCA 1 and BRCA2)*.

Exploratory Endpoints:

Baseline biomarker values from most recently obtained tumor tissue (deeply recommended from metastatic tumor) will be used for central assessment of biomarkers related to breast tumor sensitivity and/or resistance to palbociclib (e.g., Ki67, p16/CDKN2A, pRb, CyclinD and others) or breast cancer (e.g. *PTEN*, *ERBB2, BRCA1 and BRCA2)*. A whole blood sample will be collected 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 drug mechanism of action may be examined. Correlative plasma samples will be collected for exploratory analysis to analyze the pharmacodynamic (PD) treatment effects on circulating free DNA or RNA and explore specific breast cancer and efficacy predictive biomarkers (e.g. PIK3CA mutation). Sample will be collected from all patients, unless prohibited by local regulations.

Justification of Sample size determination and interim analyses:

The primary objectives of this study are to demonstrate that the combination of palbociclib and fulvestrant is superior to capecitabine in prolonging PFS in postmenopausal women with HR+/HER2- metastatic breast cancer, whose tumors are resistant to prior aromatase inhibitors (Cohort 2) and to demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging PFS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors and whose tumor had estrogen receptor (*ESR1*) mutational status as wild type at study entry (Cohort 1 + Cohort 2). All patients from Cohort 2 and patients with *ESR1* mutational status as wild type from Cohort 1 + Cohort 2 are eligible for the two primary inferential assessments of efficacy.

Cohort 2 will have an 80% power to detect a difference between the control arm with a median PFS of 6 months and the experimental arm (palbociclib plus fulvestrant) with a median PFS of 9 months, for a hazard ratio of 0.667, with a 5% significance level. Assuming a non-uniform accrual accomplished over a period of about 26 months, and a follow up period for the final PFS

analysis of about 28 months from the start of study randomization of Cohort 2, a total sample size of approximately 300 patients (150 in each treatment arm) will be required and the necessary number of events for the final PFS analysis is determined to be 193.

Cohort 1 + Cohort 2 (*ESR1* wild type) should have an approximately 80% power to detect a difference between the control arm with a median PFS of 6 months and the experimental arm (palbociclib plus fulvestrant or exemestane) with a median PFS of 9 months, for a hazard ratio of 0.667, with a 5% significance level in *ESR1* mutation status as wild type patients. The sample size will be similar to Cohort 2. Approximately 308 patients and 193 PFS events will be accumulated if we assume 80% cDNA collection/detect rate and 70% of patients will have tumors with *ESR1* mutational status as wild type at study entry (approximately 140 mutational status as wild type from 250 patients from Cohort 1 and 168 mutational status as wild type from 300 patients from Cohort 2).

The study is designed to have two interim analyses and the final analysis based on the primary endpoint of PFS. The first interim analysis will be performed after approximately 150 patients have documented progressive disease or death in Cohort 1 and only patients randomized to Cohort 1 will be included. The enrollment of Cohort 2 will not be affected by the outcome of the first interim analysis. The purposes for the first interim analyses are to assess the safety of the patients and to potentially re-evaluate the assumption of the proportion of patients with ESR1 wild type randomized to the study which may affect the sample size determination for Cohort 1 + Cohort 2 (*ESR1* wild type) analyses. The second interim analysis will be performed on Cohort 2 and Cohort 1 + Cohort 2 (*ESR1* wild type) after approximately 116 patients have documented progressive disease or death in Cohort 2 (approximately 60% of the total events expected for Cohort 2). The purposes for the second interim analyses are to allow for early stopping of the study for efficacy, futility, to assess the safety of the combination regimens and to potentially re-estimate the sample size of the trial. The significance level will be allocated to the second interim and final analyses with a Bonferroni method, such as alpha=0.002 for the second interim analysis, and alpha=0.048 for the final analysis.

The sample size described above will also allow the assessment of differences in the secondary endpoint of overall survival (OS). The median OS for women with advanced or metastatic breast cancer treated with capecitabine is assumed to be 22 months. With an overall significance level of 10% and one interim analysis of OS (at the time of PFS final analysis), Cohort 2 will have approximately 80% power to detect a hazard ratio of 0.667 (representing a 50% increase in median OS from 22 months to 33 months) when approximately 152 deaths have occurred after an approximate follow up of 50 months from the start of study randomization of Cohort 2. Similar sample size determination also applies to Cohort 1 + Cohort 2 (*ESR1* wild type).

An early safety review has been performed by the external Independent Data Monitoring Committee (IDMC) recommending continuing the study as planned. In addition, the interim PFS analyses will provide the potential to identify early any unexpected safety issues associated with the palbociclib combinations.

Additionaly a planned PK sub-study of the palbociclib and exemestane combination has been performed showing a lack of a clinically meaningful drug-drug interaction (DDI) between

palbociclib and exemestane when administered in combination.

Statistical:

- Demographics and Baseline Characteristics

  Standard descriptive statistics, such as the mean, median, range and proportion, will be used to summarize the patient sample and to estimate parameters of interest. Ninety-five percent confidence intervals will be provided for estimates of interest wherever possible.

- Safety Analyses

  Adverse events data and serious adverse events will be reported in frequency tables (overall and by intensity). The safety analysis will be performed in the population that has received at least one dose of the drugs.

- Efficacy Analyses

  PFS, CBR, and OS will be evaluated in the ITT and *ESR1* wild type populations. ORR, will be evaluated in the ITT and *ESR1* wild type populations with measurable disease, RD will be evaluated in the responding patients.

  A modification of Hochberg's method will be used for the two primary treatment comparisons to provide control of experiment-wise Type 1 error at a 5% significance level. With this closed testing method, statistical significance applies to both p_1 for Cohort 2 and p_2 for Cohort 1 + Cohort 2 (*ESR1* wild type) if $p_1<0.05$ and $p_2<0.05$; or it applies only to Cohort 2 if $p_1\leq0.025$ when Cohort 1 + Cohort 2 (*ESR1* wild type) has $p_2>0.05$; or it applies only to Cohort 1 + Cohort 2 (*ESR1* wild type) if $p_2\leq0.025$ when Cohort 2 has $p_1>0.05$ (assuming the analyses results represented by both p_1 for Cohort 2 and p_2 for Cohort 1 + Cohort 2 (ESR1 wild type) demonstrate that the combination of palbociclib and fulvestrant and palbociclib and endocrine therapy respectively are superior to capecitabine in prolonging PFS).

Study population and main inclusion and exclusion criteria:

Patients with hormonal receptor positive and HER2 negative MBC who are resistant to prior AI therapy.

Inclusion Criteria:

Patients are eligible to be included in the study only if they **meet all** of the following criteria:

1. The patient has signed the informed consent document.
2. a) *Patients included in Cohort 1*: Females with histologically confirmed MBC whose disease was resistant to previous non-steroidal aromatase inhibitors (letrozole or anastrozole), defined as:
   - ✓ Recurrence while on or within 12 months after the end of adjuvant treatment with non-steroidal aromatase inhibitors (NSAI) or
   - ✓ Progression while on or within 1 month after the end of treatment with NSAI for

advanced disease.

b) *Patients included in Cohort 2*: Females with histologically confirmed MBC whose disease was resistant to previous aromatase inhibitors (exemestane, letrozole or anastrozole), defined as:

- ✓ Recurrence while on or within 12 months after the end of adjuvant treatment with an AI or
- ✓ Progression while on or within 1 month after the end of treatment with an AI for advanced disease.

3. Previous chemotherapy is permitted either in the (neo)adjuvant setting and/or first line therapy for MBC (chemotherapy administered as "second adjuvant therapy" for locoregional recurrence should be considered as first line chemotherapy for MBC).
4. It is not mandatory to have exemestane, letrozole or anastrozole as the most recent treatment before randomization but recurrence or progression of breast cancer while receiving or after the end of (in the mestastatic setting *immediately* after the end of) the most recent systemic therapy has to be documented before randomization.
5. Hormonal receptor positive (HR+) breast cancer based on local laboratory determination. HR+ defined as ≥ 1% positive cells by IHC for ER and/or PgR.
6. Documented HER2 negative breast cancer based on local laboratory determination on most recent tumor biopsy. HER2 negative tumor is determined according to recommendations of ASCO/CAP 2013 guidelines, as IHC score 0 or 1+ or negative by ISH (FISH/CISH/SISH) defined as a HER2/CEP17 ratio < 2 with an average HER2 copy number <4.0 or for single probe assessment a HER2 copy number < 4.
7. Measurable disease or at least one bone lesion, lytic or mixed (lytic+blastic), which has not been previously irradiated and is assessable by CT/MRI in the absence of measurable disease according to RECIST 1.1 criteria.
8. Patient is at least 18 years of age.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1.
10. Life expectancy ≥ 12 weeks.
11. Adequate organ and bone marrow function defined as follows:
    - ✓ ANC ≥ 1,500/mm^3 ($1.5x10^9$/L)
    - ✓ Platelets ≥ 100,000/mm^3 ($100x10^9$/L)
    - ✓ Hemoglobin ≥ 9g/dL (90g/L)
    - ✓ Serum creatinine ≤ 1,5xULN and estimated creatinine clearance ≥ 60 mL/min as calculated using the standard method for the institution
    - ✓ Total serum bilirubin ≤ 1,5xULN (≤ 3.0xULN if Gilbert´s disease)
    - ✓ AST and ALT ≤ 3.0xULN (≤5.0xULN if liver metastases present)
    - ✓ Alkaline phosphatase ≤ 2.5xULN (≤5.0xULN if bone or liver metastases present)
12. Postmenopausal women defined as women with:

- ✓ Prior bilateral surgical oophorectomy, or
- ✓ Age ≥ 60 years
- ✓ Age < 60 year and medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause or follicle-stimulating hormone (FSH) and estradiol blood levels in their respective postmenopausal ranges.

13. 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).
14. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

Exclusion Criteria:

Patients will be excluded from the study if they **meet any** of the following criteria:

1. Have received more than 1 prior chemotherapy regimen for MBC. (NOTE: Chemotherapy administered as "second adjuvant therapy" for locoregional recurrence should be considered one prior chemotherapy for MBC). Other previous anticancer endocrine treatments for advanced disease are allowed.
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 treatment with any CDK4/6, mTOR or PI3K inhibitor [any agent whose mechanism of action is to inhibit the PI3 kinase-mTOR pathway] or capecitabine.
5. a) Patients included in Cohort 1: Prior treatment with exemestane in the metastatic setting. If the patient has received exemestane in the adjuvant setting and developed MBC, she will be eligible for the study provided:
   - ✓ She has received letrozole/anastrozole as first-line MBC and progressed.
   - ✓ At least 1 year has elapsed since the end of adjuvant exemestane treatment.

   b) Patients included in Cohort 2: Prior treatment with fulvestrant in the metastatic setting. If the patient has received fulvestrant in the adjuvant setting and developed MBC, she will be eligible for the study provided:

- ✓ She has received letrozole/anastrozole/exemestane as first-line MBC and progressed.
- ✓ At least 1 year has elapsed since the end of adjuvant fulvestrant treatment.

6. Patients treated within the last 7 days prior to randomization with:
   - ✓ Food or drugs that are known to be CYP3A4 inhibitors
   - ✓ Drugs that are known to be CYP3A4 inducers
   - ✓ Drugs that are known to prolong the QT interval
7. Patients who received before randomization:
   - ✓ Any investigational agent within 4 weeks.
   - ✓ Chemotherapy within a period of time that is < the cycle length used for that treatment (e.g. < 3 weeks for fluorouracil, doxorubicine, epirubicin or < 1 week for weekly chemotherapy).
   - ✓ Previous endocrine therapy is permitted without any window.
   - ✓ Radiotherapy within 2 weeks (all acute toxic effects must be resolved to NCI CTCAE version 4.0 grades <1, except toxicities not considered a safety risk for the patient at investigator´s discretion) but patients who received prior radiotherapy to >25% of bone marrow are not eligible independent of when it was received.
   - ✓ Major surgery or other anti-cancer therapy not previously specified within 4 weeks: all acute toxic effects must be resolved to NCI CTCAE version 4.0 grades < 1, except toxicities not considered a safety risk for the patient at investigator´s discretion.
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 > 480msec, 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. Difficulties to swallow tablets, malabsorption syndrome disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or active inflammatory bowel disease or chronic diarrhea.
13. Known hypersensitivity to palbociclib, capecitabine or to exemestane (patients of cohort 1) or to fulvestrant (patients of cohort 2) or any of their excipients.

14. Any of the following contraindications for chemotherapy with capecitabine:
    - ✓ Known deficiency or family history of deficiency of dihydropyrimidine dehydrogenase.
    - ✓ Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine.
15. Only for patients in Cohort 2 any of the following contraindications for treatment with fulvestrant:
    - ✓ Bleeding diathesis (i.e., disseminated intravascular coagulation [DIC], clotting factor deficiency) or long-term (>6 months) anticoagulant therapy other than antiplatelet therapy and low dose coumarin derivatives, provided that the International Normalised Ratio (INR) is less than 1.6.
16. Known human immunodeficiency virus infection.
17. 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.
18. Recent or active suicidal ideation or behavior.

Table of Contents

Abbreviations and Definitions

ABC	Advanced Breast Cancer
AE	Adverse Event
AI	Aromatase Inhibitor
ALT/ALAT (SGPT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
AR	Adverse Reaction
ASCO	American Society of Clinical Oncology
AST/ASAT (SGOT)	Aspartate Aminotransferase
AUC	Area Under the Curve
CAP	College of American Pathologist
cDNA	Circulating free DNA
CDK	Cyclin-Dependent Kinase
CISH	Chromogenic In Situ Hybridization
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CT Scan	Computed Tomography Scan
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form (sometimes referred to as Clinical Report Form). An electronic form for recording study participants' data during a clinical study, as required by the protocol.
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
End of Study (Trial)	The end of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.

Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned a registration number and treatment.
Enter	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.
ER	Estrogen Receptor
ERB/IRB	Ethical review board/Institutional review board: A board or committee (institutional, regional, or national) composed of medical professional and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
ESR	Expedited Safety Report
ESR1	Estrogen Receptor 1
ER-LBD	Estrogen Receptor-Ligand Binding Domain
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GEICAM	Spanish Breast Cancer Research Group
G-CSF	Granulocyte Colony-Stimulating Factor
GI	GastroIntestinal
HER2	Human Epidermal Growth Factor Receptor 2
Hgb	Hemoglobin
HR	Hormonal Receptor
ICD	Informed Consent Document
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

ISH	In Situ Hybridization
ITT	Intent To Treat
Legal Representative	An individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial.
LLN	Lower Limit of Normal
LFT	Liver Function test
MBC	Metastatic Breast Cancer
MID	Minimally important difference
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NCI	National Cancer Institute
NSAI	Non-Steroidal Aromatase Inhibitor
ORR	Objective Response Rate
OS	Overall Survival
Patient	A subject with a defined disease.
PD	Progressive Disease or Pharmacodynamic depending on the context
PFS	Progression-Free Survival
PgR	Progesterone Receptor
PK	Pharmacokinetic
PR	Partial Response
QD	Once A Day
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
RR	Response Rate
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAI	Steroidal aromatase inhibitor

SC	Steering Committee
SD	Stable Disease
SISH	Silver In Situ Hybridization
SOP	Standard Operating Procedure
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TdP	Torsade de Pointes
TEAE	Treatment-Emergent Adverse Event
TTP	Time To Progression
ULN	Upper Limit of Normal
WNL	Within Normal Limits

Phase III study of Palbociclib (PD-0332991) in combination with Endocrine therapy (exemestane or fulvestrant) versus chemotherapy (capecitabine) in Hormonal Receptor (HR) positive/HER2 negative Metastatic Breast Cancer (MBC) patients with Resistance to Aromatase inhibitors "The PEARL study"

1. Introduction

1.1. Overview of Breast Cancer

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 months (2) and the medical need for more active agents in this clinical setting remains very high.

1.2. Treatment options for Hormonal Receptor (HR) positive patients resistant to an AI

Approximately two-thirds of breast cancers express estrogen receptor (ER) (3) and the role for estrogens in breast cancer etiology and progression is well established. Endocrine therapy is the treatment of choice for most women with metastatic hormone receptor (HR) positive breast cancer. It is an effective treatment with a relatively low toxicity that enables preservation of quality of life. For many years tamoxifen was the gold standard for first-line therapy, but in postmenopausal women aromatase inhibitors or 'inactivators' have been shown to be superior (4).

In postmenopausal women, the synthesis of estrogen takes place almost exclusively in extra-ovarian tissues, with the conversion of androstenedione to estrone in the peripheral adipose tissue. Aromatase inhibitors prevent the cytochrome p-450 aromatase enzyme from catalysing the steroid hydroxylation reactions involved in the conversion of androstenedione to estrone. The first developed aromatase inhibitor was aminoglutethimide, which proved to be at least as effective as tamoxifen, but with significant toxicities of drowsiness and rash (5). Second-generation aromatase inhibitors (formestane and fadrozole) were developed to have improved specificity for the aromatase enzyme and were soon superseded by third-generation compounds with greater specificity, potency, bioavailability and tolerability.

The three commonly used third-generation aromatase inhibitors (anastrozole, letrozole and exemestane) differ between each other with respect to basic pharmacological characteristics and can be divided according to whether they are nonsteroidal (NSAIs; with a reversible

mechanism of action) or steroidal (SAIs; with an irreversible mechanism of action). Only exemestane is steroidal and binds irreversibly to aromatase to compete with the precursors of estrogen for the enzyme.

The most effective sequence of tamoxifen and both SAIs and NSAIs has been extensively studied in the adjuvant setting. Unfortunately, not all patients respond to endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance). The treatments options for women with early disease recurrence or progression to initial NSAI therapy have received relatively little attention. Patients with strongly estrogen receptor/progesterone receptor-expressing tumors might benefit more from alternative endocrine therapy, including SAIs (exemestane) and the estrogen-receptor (ER) down-regulator fulvestrant. Exemestane was studied in this setting in several trials from which only 2 were randomized and reported information about Time to Progression (TTP) or Progression Free Survival (PFS), which was ranging between 2.8 to 3.7 months (6,7). In the EFECT study, Fulvestrant with a loading-dose regimen (500 mg on day 0, 250 mg on days 14, 28, and 250 mg every 28 days thereafter) was compared with exemestane in 693 women with HR positive advanced breast cancer (ABC) progressing or recurring after nonsteroidal AIs. Median TTP was 3.7 months in both groups (hazard ratio: 0.963; 95% CI: 0.819 to 1.133; p=0.6531). The overall response rate (7.4% v 6.7%; p=0.736) and clinical benefit rate (32.2% v 31.5%; p=0.853) were similar between fulvestrant and exemestane respectively. Median duration of clinical benefit was 9.3 and 8.3 months, respectively (6). However, there is evidence to suggest that doses of fulvestrant higher than 250mg may have greater pharmacodynamic activity against the ER pathway. A phase III clinical trial [CONFIRM trial] was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The results of a trial comparing 250 mg of fulvestrant to high-dose fulvestrant (500 mg monthly), showed a median PFS for 500mg of 6.5 months compared to 5.5 months for 250mg (hazard ratio: 0.63; 95%CI, 0.39 to 1.00; p-value 0.0496). Median OS was 26.4 months for 500mg versus 22.3 months for 250mg (hazard ratio: 0.81, CI95%: 0.69, 0.96; p-value 0.016), but we have to take into consideration that less than half of the patients in this trial had previously received an AI (8-9). Also, a pilot Japanese study showed that fulvestrant at the 500mg dose resulted in plasma levels approximately double those seen with 250mg fulvestrant (10). Additionally, a neoadjuvant study comparing fulvestrant low-dose and high-dose reported a significantly greater Ki67 and ER downregulation with the high-dose compared with the low-dose regimen (11).

Taking into account those disappointing results most clinicians would think about recommending chemotherapy for their patients resistant to AIs. In a recently published study, the median PFS in patients with HR-positive disease with the administration of capecitabine and taxanes or anthracyclines as first-line therapy, was 6.2 and 8.2 months respectively (12). An additional trial also published recently showed a median PFS of 6 months in patients with HR-positive disease when treated with several chemotherapy options in second line (13).

In addition to the administration of chemotherapy, there is a huge investment in the identification of new therapeutic strategies that would enhance the efficacy of endocrine therapies.

To date only one drug, Everolimus (Afinitor®), has been successful in this fight, and is already approved by the most relevant regulatory Agencies for patients that have received previously an AI.

Everolimus is a rapamycin derivative that inhibits mTOR [one of the pathways thought to be implicated in both the primary or acquired resistance to hormonal therapy (14)] through allosteric binding to mTORC1 (15).

In preclinical models, the use of everolimus in combination with AIs resulted in synergistic inhibition of the proliferation and induction of apoptosis (16). In a randomized, phase II study comparing neoadjuvant everolimus plus letrozole with letrozole alone in patients with newly diagnosed ER-positive breast cancer, the response rate for the combination was higher than that for letrozole alone (17).

Based on this data, the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study evaluated the efficacy and safety of the combination of everolimus and exemestane in patients with HR-positive breast cancer refractory to NSAIs (7). The interim results from this trial showed that the median PFS according to the investigator assessment for everolimus plus exemestane was 6.9 months, more than 2-fold that for the exemestane plus placebo (2.8 months), with a hazard ratio for progression or death of 0.43 (95% confidence interval [CI], 0.35 to 0.54; P<0.001). The median PFS according to central assessment was 10.6 months and 4.1 months, respectively (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; P<0.001). The most common grade 3 or 4 adverse events were stomatitis (8% in the everolimus-plus- exemestane group vs. 1% in the placebo-plus-exemestane group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%) and pneumonitis (3% vs. 0%). In addition, serious adverse events, were reported among 23% of patients in the combination-therapy group (11% attributed to study treatment) and 12% in the exemestane-alone group (1% attributed to study treatment). A higher percentage of patients discontinued everolimus in the combination-therapy group than discontinued placebo in the control group because of adverse events (19% vs. 4%) and withdrawal of consent (5% vs. 2%). For exemestane discontinuation, the corresponding numbers were 7% versus 3% and 7% versus 2%.

This was a perfect proof of concept trial but did not solve the definitive question of what can everolimus offer in these AIs resistant patients, because most physicians would not have administered exemestane monotherapy but chemotherapy to these patients, implying that the control arm was not the most appropriate one and leaving the role of everolimus treatment in this patient population ill-defined.

1.3. Role of Capecitabine in the Treatment of HR-positive Metastatic Breast Cancer

Capecitabine (Xeloda®; F. Hoffmann-La Roche, Basel, Switzerland) is an oral antimetabolite of the fluoropyrimidine family that is converted to 5-fluorouracil in a three-step enzymatic

process. The final step is catalyzed by the thymidine phosphorylase (TP) enzyme, whose quantity and function are increased in various tumor types, including breast cancer, compared with adjacent healthy tissue (18). Final activation of capecitabine to 5-fluorouracil therefore occurs preferentially in the tumor cells and limits the appearance of adverse effects in other organs (19,20).

Capecitabine is approved in more than 90 countries as single agent in patients who previously failed to paclitaxel and anthracyclines, or who cannot receive these drugs (21). Capecitabine in combination with docetaxel is also approved for advanced breast cancer patients who have experienced treatment failure with anthracyclines.

Capecitabine is currently considered to be one of the most active drugs available in advanced breast cancer, and its efficacy has been amply demonstrated in monotherapy in either previously treated patients or as first-line therapy for metastatic disease (22-26). When administered alone in previously treated patients, capecitabine efficacy achieved median TTP/PFS ranging from 2.8 to 5.9 months (which increased in patients with HR-positive disease) and overall survival times of 9.3 to 18.1 months (27).

The capecitabine label recommends a dose in monotherapy for advanced breast cancer patients of 1250 mg/m^2 twice daily, on days 1 to 14 of every 21-day period (21). Administered at these doses and according to this regimen, capecitabine shows a toxicity profile with undesirable adverse effects, with the most frequent being Grade 3 or 4 hand-foot syndrome (16%), diarrhea (10%), fatigue (5%), stomatitis (3%), and vomiting (3%) (27).

Based on these data we selected capecitabine for our control arm for this study.

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

Studies of ER-positive breast cancer cell lines indicate that estrogens (28) and antiestrogens (29) 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 (30-33). 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 (33).

D-type cyclins play an essential role in recognition of extracellular growth stimuli and initiation of G1 transit (34,35), 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 (36-39). Expression of cyclin D1 in breast tumor isolates correlates with ER-positive status (40-42). 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 (43-46). Estrogen-induced S-phase entry in these cells is inhibited by microinjection of antibodies to cyclin D1 (47). Antiestrogen-induced growth arrest of ER-positive breast cancer cells is associated with decreased cyclin D1 expression (48). Collectively, these studies are consistent with a model of estrogen action in which the 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 (49-52).

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 p16INK4a (35,53-56). 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 (57-59). Over expression of p16INK4a in cells with functional pRb results in inhibition of both CDK4-and CDK6-associated kinase activity and pRb phosphorylation, with subsequent cell cycle arrest (57,58). In addition, inhibition of D-type cyclin-CDK4 complex formation by p16INK4a prevents sequestration of p21Cip1 and p27Kip1 by these complexes in early G1, leading to suppression of cyclin E-CDK2 activity (60-62).

Overexpression of p16INK4a through adenoviral transduction of CDKN2A into MCF-7 cells leads to G1 arrest associated with inhibited CDK activity (63,64). Cell cycle progression induced by estradiol requires action of the steroid through mid-G1, well beyond the point of cyclin D1-CDK4 activation (44). Functional association of cyclin D1-CDK4 is required for estrogen-induced CDK2 activation and G1/S transition and estrogen regulates expression of p21Cip1, p27Kip1, and Cdc25A independent of D-type cyclin-CDK4 function (65).

1.5. 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 (66-68), while the majority of human mammary carcinomas over express cyclin D1 protein (69-71). 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 (69,72). 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 (73,74). 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 (75). The continued presence of CDK4-associated kinase activity is actually required to maintain breast tumorigenesis (76). 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 (77-80). In preclinical models, Rb depletion appears to be associated with resistance to antiestrogen therapy (81). Finally, virtually all ER-positive cell lines harbor loss of p16INK4a (82-83) 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.

1.6. Overview of Palbociclib

Palbociclib (Molecular Weight: 447.53) is an orally active potent and highly selective reversible inhibitor of CDK4 and CDK6. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase.

1.6.1. Preclinical Data

Treatment of cultured tumor cells with palbociclib 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.

Palbociclib 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 palbociclib (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 (84).

The combination of palbociclib with tamoxifen has recently been tested in vitro in ER+ human breast cancer cell lines indicating a synergistic interaction (84) and provides a biologic rationale for evaluating the combination of palbociclib with anti-hormonal therapy in the clinic. Also, recently data from Julie Kan´s group in hormone resistant models (MCF7-CYP19) indicate a significant benefit of the combination of palbociclib and letrozole as well as palbociclib and fulvestrant over the single agents letrozole and fulvestrant (Pfizer, unpublished data).

1.6.2. Human Pharmacokinetic (PK) Data (85)

Single-Dose Pharmacokinetics

The single-dose pharmacokinetics (PK) of palbociclib have been evaluated in a total of 24 clinical studies, of which 3 were conducted in patients with advanced malignant disease (Studies A5481001, A5481010 and A5481019) and 21 were conducted in healthy subjects (Studies A5481009, A5481011, A5481013 [also included subjects with hepatic impairment], A5481014 [also included subjects with renal impairment], A5481015, A5481016, A5481017, A5481018, A5481020, A5481021, A5481022, A5481026, A5481032, A5481036, A5481038,

A5481039, A5481040, A5481041, A5481079, A548081 and 5481091). Among these studies, 2 studies in healthy subjects (Studies A5481009 and A5481011) also evaluated PK of PF-05089326, the active lactam metabolite of palbociclib, after administration of a single palbociclib dose.

Patients With Advanced Malignant Disease: Single dose PK was evaluated in patients with advanced malignant disease following doses ranging from 25 mg to 225 mg in Study A5481001, which was an open-label, noncomparative, dose-finding, first in patients study. Following administration of a single 125 mg dose of palbociclib, the median time of maximum concentration (T_{max}) was observed at 7 hours post-dose. Palbociclib AUC_{inf} and $t_{½}$ could not be estimated after single-dose administration in this study, because the last blood samples for PK evaluations were obtained at 10 hours after dosing. The palbociclib geometric mean C_{max} was 42.7 ng/mL after palbociclib single-dose administration to fasting patients and 59.1 ng/mL after palbociclib single-dose administration to fed patients in the food effect portion of Study A5481001 after normalizing for a 125 mg dose. The geometric mean $AUC_{(0-10)}$ was 290 ng•hr/mL in fasting patients and 371 ng•hr/mL in fed patients after normalizing for a 125 mg dose. These results 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.

Single dose PK was also evaluated in patients with advanced malignant disease following doses of 100 mg and 125 mg in Study A5481010, which was an open-label, noncomparative, dose-finding, first in a Japanese patients study. After a single 125-mg palbociclib dose in Study 1010, median T_{max} was 4 hours, the geometric mean C_{max} was 104 ng/mL, the geometric mean AUC_{inf} was 2483 ng•hr/mL, and median $t_{½}$ was 23.9 hours.

Single dose PK was also evaluated in patients with ER-positive, HER2-negative advanced breast cancer following a dose of 125 mg in Study A5481019, which was an open-label, noncomparative, PK bridging study in Chinese patients. Following administration of a single 125 mg dose of palbociclib, the median Tmax was 8 hours, the geometric mean C_{max} was 82.1 ng/mL, the geometric mean AUC_{inf} was 2386 ng•hr/mL, and median t½ was 23.5 hours.

Healthy Subjects: As of the data cutoff date of 31 August 2017, single dose PK profiles have been collected from 550 healthy volunteers following 1350 doses of palbociclib ranging from 50 mg to 150 mg. Palbociclib PK profiles and parameters following single 125 mg doses appeared to be generally comparable across studies conducted in healthy subjects. After a single oral 125 mg dose of palbociclib, the median Tmax was observed between 6 hours and 8 hours after oral dosing. Following attainment of Cmax, plasma palbociclib concentrations declined in a multiexponential manner, with mean t½ values ranging between 19.4 hours and 26.4 hours. The palbociclib geometric mean plasma Cmax values ranged from approximately 28.0 ng/mL to 72.1 ng/mL, while the geometric mean AUC_{inf} values ranged from 1087 ng•hr/mL to 2136 ng•hr/mL. The palbociclib geometric mean Vz/F values ranged between

1907 L and 4007 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively distributes to peripheral tissues. The palbociclib geometric mean CL/F values ranged between 58.5 L/hr and 115 L/hr.

Multiple-Dose Pharmacokinetics

The multiple-dose PK of palbociclib was evaluated in a total of 5 studies in patients with advanced solid malignant tumors (Studies A5481001, A5481003, A5481008, A5481010 and A5481019). Following repeated 125 mg QD dosing to steady state, palbociclib was absorbed with a median T_{max} ranging from approximately 4 hours to 8 hours post-dose. Palbociclib was eliminated slowly, with a mean $t_{½}$ ranging from 23.2 hours to 28.8 hours. Palbociclib accumulated after repeated dosing (median R_{ac} = 1.9 - 2.4), which was consistent with its terminal t½. The palbociclib geometric mean plasma C_{max} values ranged from 94.9 ng/mL to 186.0 ng/mL, while the geometric mean plasma AUC_{24} values ranged from 1633 ng•hr/mL to 2838 ng•hr/mL.

Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, data indicate that CYP3A and sulfotransferase (SULT) enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. An exploratory evaluation of the circulating metabolites for palbociclib was conducted in plasma samples obtained from patients treated with palbociclib 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 palbociclib and the lactam of palbociclib (PF-05089326) were the main metabolites present in plasma. Other metabolites observed were the glucuronide conjugates of hydroxylated palbociclib and the glucuronide conjugate of reduced palbociclib. PF-05089326 was also observed in the circulation of rats following repeated daily oral administration of palbociclib at the dose levels of 50 and 100 mg/kg/day. Plasma protein binding of palbociclib and PF-05089326 is ~85% and 95%, respectively.

Concomitant administration of agents which increase gastric pH can alter the solubility and absorption of palbociclib free base formulations.

Study A5481038 evaluated the effects of staggered dosing of the H2-receptor antagonist (H2RA) famotidine, and of the staggered dosing of the local antacid Mi-Acid Maximum Strength Liquid, on the PK of a single oral 125 mg palbociclib final Phase 3/commercial free base capsule given with food in healthy subjects. The results indicated that administration of palbociclib under fed conditions with staggered famotidine and staggered Mi-Acid Maximum Strength Liquid dosing had no impact on the exposure of palbociclib.

Study A5481038 also evaluated the effects the coadministration of a single 125 mg dose of the free base capsule of palbociclib following multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions in healthy volunteers. Concurrent administration of rabeprazole with palbociclib decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease) compared with a single dose of palbociclib administered alone. This 13% reduction in overall exposure is not thought to be clinically relevant.

Given the reduced effect on gastric pH of H2RAs and local antacids compared to PPIs, the effect of these classes of acid-reducing agents on palbociclib exposure under fed conditions is expected to be minimal.

PK data from Study A5481023 was analyzed to evaluate the potential for DDIs between palbociclib and fulvestrant, as well as between palbociclib and goserelin, at steady-state. These data indicate a lack of any clinically relevant DDIs between palbociclib, fulvestrant, and goserelin when administered in combination.

1.6.3. QTc Evaluation Data (85)

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. Palbociclib did not prolong QTc to any clinically relevant extent at the recommended dose of 125 mg daily

A pharmacokinetic/pharmacodynamic analysis to evaluate the relationship between palbociclib exposure and ECG endpoints (RR and QTc intervals) were developed using pooled data from 3 clinical trials in patients with advanced malignant disease (Studies A5481001, A5481002, and A5481003). The study population consisted of 48 men and 136 women with a median (range) body weight of 73.0 (37.9-123) kg and age of 61.5 (22-89) years old. Palbociclib doses ranged from 25 mg to 225 mg QD. The data collected from 184 patients consisted of 569 ECG-palbociclib concentration-matched pairs; the observed plasma concentrations had a median (range) of 55.2 (2.51-329) ng/mL. The average heart rate, RR, QT, QT corrected for heart rate according to Bazett (QTcB), QT corrected for heart rate according to Fridericia (QTcF), and QTcS (QT interval corrected for heart rate according to a study-specific correction factor) at baseline for ECG-palbociclib concentration matched data were 76.8 beats per minute, 808 msec, 380 msec, 425 msec, 409 msec, and 412 msec, respectively.

The results of the analysis indicate that palbociclib does not appear to have a concentration-dependent effect on heart rate. A slight positive linear relationship between palbociclib concentration and QTcS was observed; however, at the mean or median steady-state palbociclib Cmax following administration of the recommended clinical dose of palbociclib (125 mg QD) in patients with cancer, the upper bound of the one-sided 95% CI for the increase in QTcS fell below the threshold of 10 msec, suggesting that QT prolongation is not a safety concern for palbociclib at the recommended clinical dose according to the criteria described in the ICH guidance for Industry E14. Similar results were obtained when QTcF and QTcB were used.

In Study A5481023 in women with breast cancer treated with palbociclib or placebo in combination with fulvestrant, no notable differences were seen between baseline and end-of treatment in the mean and median values for RR interval, heart rate, QT interval, QTcB interval, and QTcF interval, in either treatment arm. There were also no relevant differences between treatment arms for any of the ECG parameters. The mean and median changes from

baseline to any post-baseline timepoint were generally minor for all parameters and did not show any relevant differences between treatment arms. None of the patients in either treatment arm showed post-baseline ECG findings of a maximum QT interval ≥500 ms. The percentage of patients with postbaseline QTcB interval ≥500 ms was slightly higher in the palbociclib plus fulvestrant arm than in the placebo plus fulvestrant arm (5.5% vs 1.4%).

Post-baseline QTcF intervals ≥500 ms were not observed in any patient in the palbociclib plus fulvestrant arm, and were observed in 1 (1.4%) patient in the placebo plus fulvestrant arm.

1.6.4. Palbociclib Dose Rationale (85)

Palbociclib has been tested in a Phase I 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 was 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.

1.6.5. Palbociclib data in Combination with Letrozole in Advanced Breast Cancer

Based on the preclinical evidence that palbociclib 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 I/II Study (A5481003 better known as PALOMA-1) was designed to assess the efficacy, safety and pharmacokinetics of letrozole 2.5mg QD (continuously) in combination with palbociclib 125mg QD (schedule 3/1) versus single agent letrozole 2.5mg 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. Patients were stratified by disease site and disease-free interval.

Study PALOMA-1 was comprised of a limited Phase I portion, aimed at confirming the safety and tolerability of the combination and excluding a PK interaction with the combination, and a randomized Phase II portion aimed at evaluating the efficacy and safety of letrozole in combination with palbociclib when compared to letrozole alone in the first-line treatment of postmenopausal patients with ER(+), HER2(-) ABC. The Phase II 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 tumors with amplification of cyclin D1 (CCND1) and/or loss of p16 (INK4A or CDKN2A), or both. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. Accrual to Cohort 2 was stopped after an unplanned interim analysis of Cohort 1 and the statistical analysis plan for the primary endpoint was amended to a combined analysis of Cohorts 1 and 2 (instead of Cohort 2 alone).

Enrollment was closed with 177 patients included in this study. Twelve were enrolled in the Phase I portion and 165 (66 and 99 in Part 1 and 2, respectively) were enrolled in the Phase II portion.

The Phase I portion included a two-way DDI assessment between palbociclib (125 mg QD, 3/1 schedule) and letrozole (2.5mg QD, continuously) and showed no PK interaction between palbociclib and letrozole (86). The exposure of palbociclib was similar in the absence and presence of letrozole. In addition, the exposure of letrozole was similar in the absence and presence of palbociclib. Therefore, there is no meaningful metabolic drug interaction. The RP2D was determined to be 125mg QD on Schedule 3/1 (3 weeks continuous treatment followed by 1 week off treatment) in combination with letrozole 2.5mg QD continuously. Partial responses were reported for 4 (33%) patients with measurable disease. Another 6 patients (50%) had stable disease for ≥ 24 weeks and the clinical benefit rate (PR + SD ≥ 24 weeks) was 83%. Eight (66.7%) patients discontinued from the study due to disease progression, including 2 patients with clinical progression, 1 patient withdrew consent and 3 patients are still ongoing.

The phase II portion randomized 165 patients, 84 to palbociclib plus letrozole and 81 to letrozole alone. At the time of the final analysis for progression-free survival (median follow up 29.6 months [95% CI 27.9–36.0] for the palbociclib plus letrozole group and 27.9 months [25.5–31.1] for the letrozole group), 41 progression-free survival events had occurred in the palbociclib plus letrozole group and 59 in the letrozole group. Median progression-free survival was 10.2 months (95% CI 5.7–12.6) for the letrozole group and 20.2 months (13.8–27.5) for the palbociclib plus letrozole group (hazard ratio 0.488, 95% CI 0.319–0.748; one-sided p=0.0004). In cohort 1 (n=66), median progression-free survival was 5.7 months (2.6–10.5) for the letrozole group and 26.1 months (11.2–not estimable) for the palbociclib plus letrozole group (hazard ratio 0.299, 0.156–0.572; one-sided p<0.0001); in cohort 2 (n=99), median

progression-free survival was 11.1 months (7.1–16.4) for the letrozole group and 18.1 months (13.1–27.5) for the palbociclib plus letrozole group (hazard ratio 0.508, 0.303–0.853; one-sided p=0.0046). Grade 3–4 neutropenia was reported in 45 (54%) of 83 patients in the palbociclib plus letrozole group versus one (1%) of 77 patients in the letrozole group, leucopenia in 16 (19%) versus none, and fatigue in four (4%) versus one (1%). Serious adverse events that occurred in more than one patient in the palbociclib plus letrozole group were pulmonary embolism (three [4%] patients), back pain (two [2%]), and diarrhoea (two [2%]). No cases of febrile neutropenia or neutropenia-related infections were reported during the study. Eleven (13%) patients in the palbociclib plus letrozole group and two (2%) in the letrozole group discontinued the study because of adverse events (87). Although the study was not designed to perform a formal hypothesis testing for overall survival (OS) analysis due to the small sample size, it was performed recently. Median overall survival data with 116 OS events, were 37.5 months (95% CI: 31.4, 47.8) in the palbociclib plus letrozole group and 34.5 months (95% CI: 27.4, 42.6) in the letrozole alone group (hazard ratio for death was 0.897 [95% CI: 0.623, 1.294]; two-sided p=0.281). Median OS was 37.5 vs 33.3 months (hazard ratio for death = 0.837; P= 0.280) for Part 1 and 35.1 vs 35.7 months (hazard ratio = 0.935; P= 0.388) for Part 2. 78.6% of pts in the P+L arm received post-study systemic therapy vs 86.4% in the L arm. More pts in the L arm received ≥3 lines of therapy (37% vs 18%) (102).

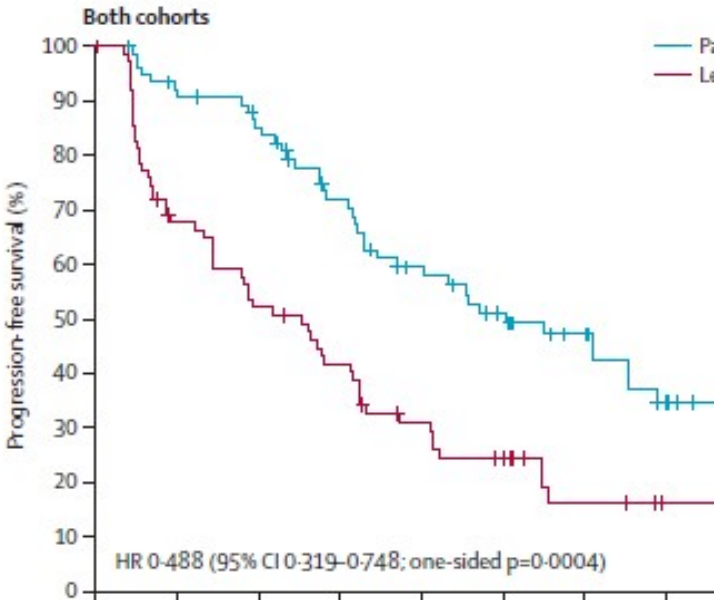
These results indicate that the combination of palbociclib with letrozole is well tolerated with AEs similar to those seen with either palbociclib or letrozole when administered alone. Additionally, the combination demonstrated antitumor activity which was consistent with the sensitivity of ER(+) breast cancer observed in the preclinical models.

These encouraging findings have been tested in a confirmatory phase III study (PALOMA-2) that included 666 postmenopausal patients with no prior systemic therapy for advanced breast cancer that were randomised 2:1 to receive palbociclib (oral 125 mg/day; 3 weeks on/1 week off) + letrozole (2.5 mg/day continuously) or placebo + letrozole every 28 days until disease progression, consent withdrawal or death. Patients were stratified by disease site, disease-free interval from end of (neo) adjuvant therapy, and prior hormone therapy (yes/no). The primary endpoint was investigator-assessed PFS, and the secondary endpoints included: overall survival, objective response rate, clinical benefit rate (CR + PR + SD ≥24 weeks), patient-reported outcomes, pharmacokinetics and safety. Baseline characteristics were well balanced between both treatment groups. Median PFS was 24.8 months (95% confidence interval [CI], 22.1 to not estimable) in the palbociclib-letrozole group, as compared with 14.5 months (95% CI, 12.9 to 17.1) in the placebo-letrozole group (hazard ratio for disease progression or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001). ORR was improved with palbociclib + letrozole (42.1% vs. 34.7%, p=0.031; 55.3% vs. 44.4% in patients with measurable disease [p=0.013]). CBR was 84.9% vs. 70.3% (p<.0001). The most common grade 3 or 4 adverse events were neutropenia (occurring in 66.4% of the patients in the palbociclib-letrozole group vs. 1.4% in the placebo-letrozole group), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%), and fatigue (1.8% vs. 0.5%). Febrile neutropenia was reported in 1.8% of patients in the palbociclib-letrozole group

and in none of the patients in the placebo-letrozole group. Permanent discontinuation of any study treatment as a result of adverse events occurred in 43 patients (9.7%) in the palbociclib-letrozole group and in 13 patients (5.9%) in the placebo-letrozole group (101). At the time of this primary analysis, the percentage of PFS events was less than 50% (43.7%) in the palbociclib plus letrozole arm. Updated PFS data based on the investigator assessment with an event rate of approximately 60% for the entire study population (55% in the palbociclib plus letrozole arm) have recently confirmed the benefit of the addition of palbociclib to letrozole with a median PFS of 27.6 months (95% CI: 22.4, 30.3) in the palbociclib plus letrozole arm and 14.5 months (95% CI: 12.3, 17.1) for the placebo plus letrozole arm. The observed hazard ratio for disease progression or death was 0.563 (95% CI: 0.461, 0.687; stratified 1-sided p<0.000001) in favor of palbociclib plus letrozole treatment (104, 105). OS data was immature in both analysis and the final OS information is still pending.

However if we pay attention to the PFS curve of PALOMA-1 study (see Figure 1), it seems to indicate that the effect of the drug on PFS was mainly due to the prevention of early progressions. In the first 4 months of the study, 40% of the patients in the letrozole arm had progressed vs only 20% in the letrozole + palbociclib arm, suggesting that the main effect of palbociclib is the reversal of resistance to the anti-hormonal treatment.

Figure 1. PALOMA-1 Progression-Free Survival



If this hypothesis is true, the inhibition of the CDK4/6 function by palbociclib in combination with anti-hormonal therapy could play an important role in ER-positive patients that have become resistant to hormones.

1.6.6. Palbociclib data in Combination with fulvestrant in Advanced Breast Cancer

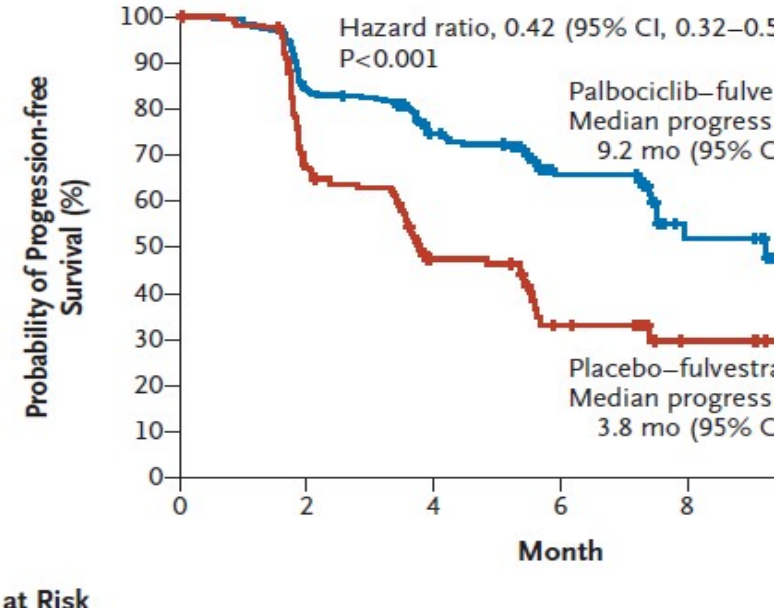
PALOMA-3 is randomized 2:1 phase III study testing the efficacy of palbociclib + fulvestrant vs fulvestrant alone (+/- Goserelin depending of menopausal status) in the treatment of breast cancer patients whose disease has progressed on endocrine therapy either within 12 months of completion of adjuvant endocrine therapy or within 1 month of endocrine therapy for advanced disease (88). The primary end point was investigator-assessed progression-free survival according to RECIST, version 1.1. Secondary end points included overall survival; survival probability at 1, 2, and 3 years; objective response; duration of response; rate of clinical benefit; patient-reported outcomes; pharmacokinetics; and safety. The trial met its primary end point at the pre-planned interim analysis (after 195 events of disease progression or death had occurred) on the basis of the recommendation by the independent data and safety monitoring committee. The median progression-free survival was 9.2 months (95% confidence interval [CI], 7.5 to not estimable) with palbociclib‑fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo‑fulvestrant (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001). Approximately 40% of the patients (211) were randomly selected for central imaging assessment by blinded independent review. The results were consistent with the primary end point; the median progression-free survival was not estimable with palbociclib‑fulvestrant and was 3.7 months (95% CI, 3.4 to 7.2) with placebo‑fulvestrant (hazard ratio for disease progression or death, 0.27; 95% CI, 0.16 to 0.46; P<0.001). Rates of overall objective response were 10.4% (95% CI, 7.4 to 14.1) with palbociclib‑fulvestrant and 6.3% (95% CI, 3.2 to 11.0) with placebo‑fulvestrant (P = 0.16). The rate of clinical benefit was 34.0% (95% CI, 29.0 to 39.3) with palbociclib‑fulvestrant and 19.0% (95% CI, 13.4 to 25.6) with placebo‑fulvestrant (P<0.001).. The most common grade 3 or 4 adverse events in the palbociclib‑fulvestrant group were neutropenia (62.0%, vs. 0.6% in the placebo‑fulvestrant group), leukopenia (25.2% vs. 0.6%), anemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Febrile neutropenia was reported in 0.6% of patients in each arm. The rate of discontinuation due to adverse events was 2.6% with palbociclib and 1.7% with placebo. Global quality of life was generally maintained with palbociclib‑fulvestrant but deteriorated significantly with placebo‑fulvestrant (mean overall change from baseline in QLQ-C30 score [range, 0 to 100, with higher scores indicating a higher quality of life], −0.9 points vs. −4.0 points; P = 0.03).

Additionally, the results of a prespecified analysis of OS in the PALOMA-3 study showed that the median OS was 34.9 months (95% CI, 28.8 to 40.0) in the palbociclib + fulvestrant group and 28.0 months (95% CI, 23.6 to 34.6) in the placebo + fulvestrant group (HR for death, 0.81; 95% CI, 0.64 to 1.03; P = 0.09; absolute difference, 6.9 months). CDK4/6 inhibitor treatment after the completion of the trial regimen occurred in 16% of the patients in the placebo–fulvestrant group. Among 410 patients with sensitivity to previous ET, the median OS was 39.7 months (95% CI, 34.8 to 45.7) in the palbociclib + fulvestrant group and 29.7 months (95% CI,

23.8 to 37.9) in the placebo + fulvestrant group (HR, 0.72; 95% CI, 0.55 to 0.94; absolute difference, 10.0 months). The median duration of subsequent therapy was similar in the two groups, and the median time to the receipt of CT was 17.6 months in the palbociclib + fulvestrant group, as compared with 8.8 months in the placebo + fulvestrant group (HR, 0.58; 95% CI, 0.47 to 0.73; P<0.001). No new safety signals were observed with 44.8 months of follow-up (106).

However if we pay attention to the PFS curve of the study (see Figure 2), it seems to indicate that the effect of the drug on PFS was mainly due to the prevention of early progressions. In the first 2 months of the study, 37% of the patients in the fulvestrant arm had progressed vs only 20% in the fulvestrant + palbociclib arm, suggesting again that the main effect of palbociclib is the reversal of resistance to the anti-hormonal treatment.

Figure 2. PALOMA-3 Progression-Free Survival



1.7. Interstitial Lung disease/pneumonitis data:

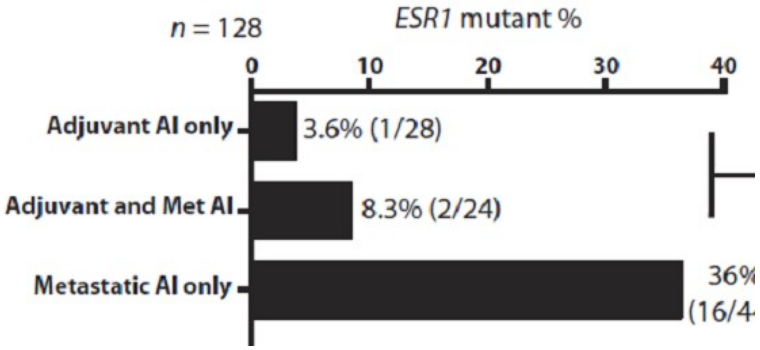
Following a recent aggregate review of cases potentially consistent with interstitial lung disease or pneumonitis mainly from post-marketing sources, but including those from clinical trials, a decision was made to consider interstitial lung disease or pneumonitis to be an adverse drug reaction of palbociclib. While a definitive causal association between palbociclib and ILD/pneumonitis could not be established, the aggregate data suggested the possibility of a causal relationship. No special precautions other than standard clinical monitoring are recommended (85).

1.8. Role of *ESR1* mutations in the mechanism of resistance to endocrine therapy

Recent studies revealed that the acquisition of mutations in the ER gene (*ESR1*) is a major mechanism of resistance to AIs.

ESR1 mutations are rarely detectable in primary breast cancer or patients that are first exposed to AIs (5.8%) and are found at an appreciable frequency and markedly higher after the AI treatment, either during the adjuvant and metastatic settings (36.4%) (89). Moreover, a high frequency of *ESR1* mutations had been reported in patients who have been treated with AIs using more contemporaneous tumor biopsy through circulating free DNA (cDNA), as can be seen in figure 3 (89).

Figure 3. *ESR1* mutations assessed in cDNA



In addition, it has been also reported a high frequency of ESR mutations detected in cDNA in the BOLERO-2 and PALOMA-3 studies. In BOLERO-2, 28.8% of the two most common subtypes (which represented 50-60% of all activating *ESR1* mutations) (90) were found in the exemestane arm among patients who progressed on NSAIs. In PALOMA-3, the detection rate of *ESR1* mutation in cDNA was 37.2% among patients who progressed on endocrine therapy (steroidal and/or non-steroidal AI for post-menopausal women) (91).

More importantly patients with *ESR1* mutations had a substantially shorter PFS on subsequent AI-based therapy what may partially explain the poor performance of sequential AI therapy in those patients. In fact Gaia Schiavon et al (89) reported that patients with *ESR1* mutations had a substantially shorter PFS on subsequent AI-based therapy (hazard ratio of 3.1, 95% CI 1.9 to 23.1; p=0.0041. Also data from BOLERO-2 presented at the SABCS 2015 showed that mPFS of exemestane in patients with *ESR1* mutation wild type (n=116) was 3.94 months vs. 2.76 months in patients with *ESR1* mutation (n=51) (hazard ratio = 1.13, p= 0.16) (90). These findings are also confirmed with data from another phase III study in the exemestane treatment arm (Turner et al, personal communication). See table 1.

Table 1. Frequency of *ESR1* mutations and performance of AI post-AI treatment in MBC setting

Study	# of Patients	*ESR1* mutation frequency post-AI	Median PFS post AI

		treatment	
Schiavon, et al (89)	171	36.4%	hazard ratio =3.1 (shorter PFS) P=0.0041
BOLERO-2 *Chandarlapaty S,* (90)	541	28.8% (two most common mutations only, represent 50-60% of all mutations)	Exemestane Arm PFS= 3.9 in wild type vs 2.7 with D538G mutation hazard ratio = 1.44

Preclinical and clinical data indicated that the ER degrader (SERD), fulvestrant, may exhibit non-cross-resistance to tamoxifen or AIs. As shown in Table 2, in the endocrine resistance setting, a number of large randomized Phase II (FERGI), 3 studies (CONFIRM, PALOMA-3, BELLE-2) have shown consistent PFS of ~ 5 to 6 months with fulvestrant 500mg. In contrast, exemestane has shown mPFS of 3-4 months (SoFEA, EFECT and BOLERO-2).

Table 2. Performance of fulvestrant 500mg and exemestane in patients who have been treated with ET

Trials	Treatment	# of Patients	Median PFS, Months
Performance of Fulvestrant 500mg			
PALOMA-3 (88)	Palbociclib + Fulvestrant vs Placebo + **Fulvestrant 500mg**	347 174	4.7
CONFIRM (9)	Fulvestrant 250 mg vs **Fulvestrant 500 mg**	374 362	6.5
FERGI (92)	GDC 0941 + Fulvestrant vs Placebo + **Fulvestrant 500mg**	84 84	5.1
BELLE-2 (93)	BKM120 + Fulvestrant vs Placebo + **Fulvestrant 500mg**	576 571	5
Performance of Exemestane			
SoFEA (94)	Fulvestrant + Anastrozole vs Fulvestrant plus placebo vs. **Exemestane**	243 231 249	3.4
BOLERO-2 (7)	Everolimus + Exemestane vs Placebo + **Exemestane**	485 239	3.2
EFECT (6)	Fulvestrant vs.	351	3.7

	Exemestane	342	

In addition, preclinical and clinical data indicated that SERD, fulvestrant, is active in *ESR1* mutant tumors. Preclinical efficacy data recently generated showed that fulvestrant is active in most common *ESR1* mutant subtypes (95) (Table 3). Also, unpublished data from PALOMA-3 suggest that there is no difference in mPFS of fulvestrant (control arm) by *ESR1* status; patients without *ESR1* mutation (n=79) had a median PFS of 114 days compared with 151 days in patients with *ESR1* mutation (n=51) (91).

Table 3. Fulvestrant in *ESR1* mutation models (Pfizer Research Unit)

Erα context	**Fulvestrant IC50 (µM)**	**FC/*ESR1***
***ESR1* wt**	0.016	–
D538G	0.279	17.4
D538G/S463P	0.199	12.4
Y537N	0.057	3.6
Y537S	0.173	10.8
Y537S.D538G	>1	>63
Y537N.S463P	0.083	5.2

Importantly, there is preclinical data showing that Palbociclib is active in multiple ERS mutant PDX models (96). This was confirmed in clinic with PALOMA-3 data. The analysis demonstrated that there was no difference in the magnitude of benefit from palbociclib in combination with fulvestrant by *ESR1* status. In patients with *ESR1* mutations, the median PFS was 9.6 months in the palbociclib arm compared with 5.0 months in the control arm (p=0.002); in patients without *ESR1* mutations, the median PFS was 11.2 months versus 3.8 months, respectively (p<0.001) (91)

However, the interim analysis from the TRend (To Reverse ENDocrine Resistance) study, where palbociclib was added to the same prior endocrine therapy agent (exemestane) vs given alone at the progression of endocrine therapy (exemestane), showed similar non-progression rates at 12 weeks between palbociclib plus endocrine therapy and palbociclib alone (per principal investigator personal communication). Although both arms were clinically active, these data suggest that there is no synergy between palbociclib and an AI (exemestane) after

progression to an AI. Thus switching to other class endocrine therapy (such as fulvestrant) in the endocrine resistance setting may be a better strategy for patients because fulvestrant is active regardless ERS1 mutational status.

1.9. Study Rationale

Endocrine therapy is the cornerstone treatment for patients with hormone-receptor (HR)–positive, HER2 negative breast cancer. In postmenopausal patients, aromatase inhibitors (e.g., letrozole and anastrozole) have become the treatment of choice. Unfortunately, not all patients respond to endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance).

On early disease recurrence/progression, the treatment options include other classes of aromatase inhibitors, estrogen-receptor (ER) antagonists or chemotherapy; being the latest the most accepted one for the resistant patients. Within the chemotherapy regimens, capecitabine seems one of the best options.

The research focusing on resistance to endocrine therapies in HR-positive breast cancer has aimed to identify new therapeutic strategies that would enhance the efficacy of endocrine therapies.

Published preclinical data suggest that estrogen receptor positive (ER-positive)/HER2 negative breast cancers are dependent on cyclin-dependent kinases 4/6 (CDK4/6) function and that inhibition of this target may be an effective translational therapeutic strategy. Palbociclib is an oral novel CDK4/6 inhibitor that seems to be synergistic with anti-hormonal therapy in preclinical and clinical studies. Results from a randomized phase II study and a phase III study of letrozole vs letrozole plus palbociclib (PALOMA-1 and PALOMA-2) confirmed the safety and tolerability of the combination and demonstrated an exciting efficacy. In addition, a further randomized 2:1 phase III study tested the efficacy of palbociclib + fulvestrant vs fulvestrant alone (+/- Goserelin depending of menopausal status) in the treatment of breast cancer patients whose disease has progressed on endocrine therapy either within 12 months of completion of adjuvant endocrine therapy or within 1 month of endocrine therapy for advanced disease (PALOMA-3 study) demonstrated an exciting efficacy with a hazard ratio for progression-free survival of 0.42 (95% CI, 0.32 to 0.56; P<0.001). The results of a prespecified analysis of OS in the PALOMA-3 study showed that the median OS was 34.9 months (95% CI, 28.8 to 40.0) in the palbociclib + fulvestrant group and 28.0 months (95% CI, 23.6 to 34.6) in the placebo + fulvestrant group (HR for death, 0.81; 95% CI, 0.64 to 1.03; P = 0.09; absolute difference, 6.9 months).

In fact based on all these data, on February the 19th 2016, the US FDA granted full approval to palbociclib (IBRANCE®) in combination with fulvestrant (with or without goserelin) for the treatment of women with HR-positive, HER2-negative advanced breast cancer whose disease progressed after prior endocrine therapy based on the favorable benefit/risk profile observed in Study PALOMA-3. In addition, on November the 9th 2016, the EU Commission decision was issued for palbociclib for the treatment of HR-positive, HER2-negative locally advanced or

metastatic breast cancer: in combination with an aromatase inhibitor or in combination with fulvestrant in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist. Additionally, palbociclib is approved in more than 80 countries globally.

The PFS curve of the two studies, however, seems to indicate that the effect of the drug was mainly due to the prevention of early progressions, suggesting that the main effect of palbociclib is the reversal of resistance to the anti-hormonal treatment. Taking all this into consideration, the combination of anti-hormonal therapy with palbociclib may play an important role in HR-positive patients that have become resistant to hormones and should be compared to the standard of care in patients with hormone-resistant HR-positive tumors, i.e. cytotoxic chemotherapy.

The initially proposed Phase III study was designed to provide the opportunity to confirm the clinical benefit of palbociclib in combination with exemestane. The study was designed to demonstrate that this combination provides superior clinical benefit compared to capecitabine in postmenopausal women with HR+/HER2- metastatic breast cancer who are resistant to non-steroidal aromatase inhibitors.

However, emerging data suggests that the choice of endocrine partner with palbociclib is particularly important to create optimal synergy in endocrine resistance setting.

Studies of resistance to hormonal therapies and ER biology have highlighted the important role of ER receptor degraders for sequential endocrine treatment after patients progressed on aromatase inhibitors (AIs). Recent studies have also revealed that the acquisition of *ESR1* mutations is a major mechanism of resistance to AIs and patients with *ESR1* mutations had a substantially shorter PFS on subsequent AI-based therapy. In addition, it has been reported a high rate of *ESR1* mutations among patients who have been treated with AIs in MBC patients. More recently, data from PALOMA-3 and other studies suggest that fulvestrant may be active among patients whose tumors had *ESR1* mutation, while exemestane is inactive (unpublished data, disclosure planned). Thus among patients who have progressed on AIs, fulvestrant may be a better endocrine partner for palbociclib.

The present trial design proposes a Phase III study to provide the opportunity to confirm the clinical benefit of palbociclib in combination with endocrine therapy. The study is designed to demonstrate that:

1) Fulvestrant plus palbociclib provides superior clinical benefit compared to capecitabine in postmenopausal women with HR+/HER2- metastatic breast cancer who are resistant to aromatase inhibitors and
2) Endocrine therapy (fulvestrant or exemestane) in combination with palbociclib provides superior clinical benefit compared to capecitabine in postmenopausal women with

HR+/HER2- metastatic breast cancer and whose tumor had estrogen receptor *(ESR1*) mutational status as wild type at study entry.

Taken all these together, the proposed amendment will allow us to address several scientific novel questions:

- The study will be able to prospectively test the hypotheses that palbociclib plus fulvestrant is superior to chemotherapy in endocrine resistance setting regardless *ESR1* mutational status as primary study objective. In the endocrine resistant setting, capecitabine, as an oral, cytotoxic chemotherapy is frequently used with mPFS at ~ 6 months but with increased toxicity and reduced quality of life.
- The study will be able to prospectively evaluate whether palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging PFS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors and whose tumors had *ESR1* mutation status as wild type at study entry.
- To our knowledge, this will be the first study prospectively testing the activity of chemotherapy by *ESR1* mutational status and compared with an emerging standard of care (palbocicilib plus fulvestrant) in this population.
- The findings will inform the clinical community if we are ready to stratify treatment by endocrine resistant mechanisms (i.e. treating patients with *ESR1* mutation with SERD in combination a CDK 4/6 inhibitor; treating patients with *ESR1* mutation wild type with AI or SERD with a CDK4/6 inhibitor; or chemotherapy by *ESR1* mutational status). This has important clinical relevance to advance our clinical care by stratifying, sequencing treatment options based on resistance mechanism while preserving best quality of life for HR+/HER2- MBC patients who have progressed on prior endocrine therapy.

2. Objectives

2.1. Primary Objectives

- To demonstrate that palbociclib in combination with fulvestrant is superior to capecitabine in prolonging Progression-Free Survival (PFS) in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors, regardless of the ESR1 mutational status.
- To demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging PFS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors and whose tumor had estrogen receptor (*ESR1*) mutational status as wild type at study entry.
  ESR1 mutational status will be determined by circulating free DNA (cDNA) and will be prospectively determined before the interims or final analyses. Patient tumor *ESR1* mutational status will be blinded to patients, investigators and study team.

2.2. Primary Endpoint

Progression-Free Survival (PFS) based on the investigator's assessment according to the RECIST version 1.1.

2.3. Secondary Objectives

- To demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging PFS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors regardless of *ESR1* mutational status at study entry.
- To demonstrate that palbociclib in combination with fulvestrant is superior to capecitabine in prolonging Overall Survival (OS) in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors.
- To demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging OS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors and whose tumor had estrogen receptor (*ESR1*) mutational status as wild type at study entry
- To demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging OS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors regardless of *ESR1* mutational status at study entry.
- To compare other efficacy measures between treatment arms: Objective Response Rate (ORR), Clinical Benefit Rate (CBR) and Response Duration (RD).
- To compare safety and tolerability between the treatment arms.

- To compare health-related quality of life between the treatment arms.
- To evaluate the Pharmacokinetics (PK) of the combination of exemestane with palbociclib (in selected sites and only in patients accepting to participate).

2.4. Secondary Endpoints

- The following efficacy endpoints will be measured:
  - Overall Survival (OS).
  - Objective Response (OR): Complete Response (CR) plus Partial Response (PR) based on the investigator's assessment according to the RECIST version 1.1 in patients randomized with measurable disease.
  - Clinical Benefit (CB): CR plus PR plus stable disease based on the investigator's assessment lasting more than 24 weeks according to the RECIST version 1.1 in all randomized patients (ITT population).
  - Response Duration (RD) based on the investigator's assessment according to the RECIST version 1.1.
- Safety will be assessed by standard clinical and laboratory tests (hematology, serum chemistry). Adverse events grade will be defined by the NCI CTCAE v4.0.
- The PK analysis will determine whether palbociclib influences the pharmacokinetics of exemestane. Blood samples will be taken at the time defined in the protocol in patients included in the experimental arm of Cohort 1 (palbociclib plus exemestane) in selected sites. Enrollment of these patients were to be finalised at the same time as completion of cohort 1 recruitment, samples from approximately 20 PK-evaluable patients were to be collected.
- The EORTC QLQ-C30, QLQ-BR23 and EQ-5D-3L questionnaires.

2.5. Exploratory Objectives

- To prospectively evaluate whether the magnitude of PFS and OS prolongation of palbociclib in combination with fulvestrant is the same in patients with *ESR1* mutational status as wild type and patients with *ESR1* mutational status positive at study entry.
- To prospectively evaluate whether PFS and OS of palbociclib in combination with exemestane is better among those patients with *ESR1* mutational status as wild type than those patients with *ESR1* mutational status positive at study entry.
- To prospectively evaluate PFS and OS of capecitabine by *ESR1* mutational status.
- To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle (e.g, CCND1 amplification, CDKN2A deletion), drug targets (e.g. CDK 4/6), tumor

sensitivity and/or resistance (e.g. Ki67, pRb, PIK3CA mutation, CCNE1 expression) or breast cancer (e.g. PTEN, *ERBB2, BRCA 1 and BRCA2)*.

2.6. Exploratory Endpoints

- Baseline biomarker values from most recently obtained tumor tissue (deeply recommended from metastatic tumor) will be used for central assessment of biomarkers related to breast tumor sensitivity and/or resistance to palbociclib (e.g., Ki67, p16/CDKN2A, pRb, CyclinD and others) or breast cancer (e.g. *PTEN*, *ERBB2, BRCA 1 and BRCA2)*. A whole blood sample will be collected 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.Correlative plasma samples will be collected for exploratory analysis to analyze the pharmacodynamic (PD) treatment effects on circulating free DNA or RNA explore specific breast cancer and efficacy predictive biomarkers (e.g. PIK3CA mutations). Samples will be collected from all patients, unless prohibited by local regulations.

3. Investigational Plan

3.1. Study Design

This is an international, multicenter, open label, controlled, randomized phase III study comparing the efficacy and safety of palbociclib in combination with endocrine therapy (exemestane or fulvestrant) versus capecitabine in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to previous aromatase inhibitors (exemestane, letrozole or anastrozole), defined as recurrence while on or within 12 months after the end of adjuvant treatment or progression while on or within 1 month after the end of treatment for advanced disease. It is not mandatory to have exemestane, letrozole or anastrozole as the most recent treatment before randomization but recurrence or progression while receiving (or immediately after the end of) the most recent systemic therapy has to be documented before randomization. Patients must have measurable disease or at least one bone lesion, lytic or mixed (lytic + blastic), which has not been previously irradiated and is assessable by CT/MRI in the absence of measurable disease.

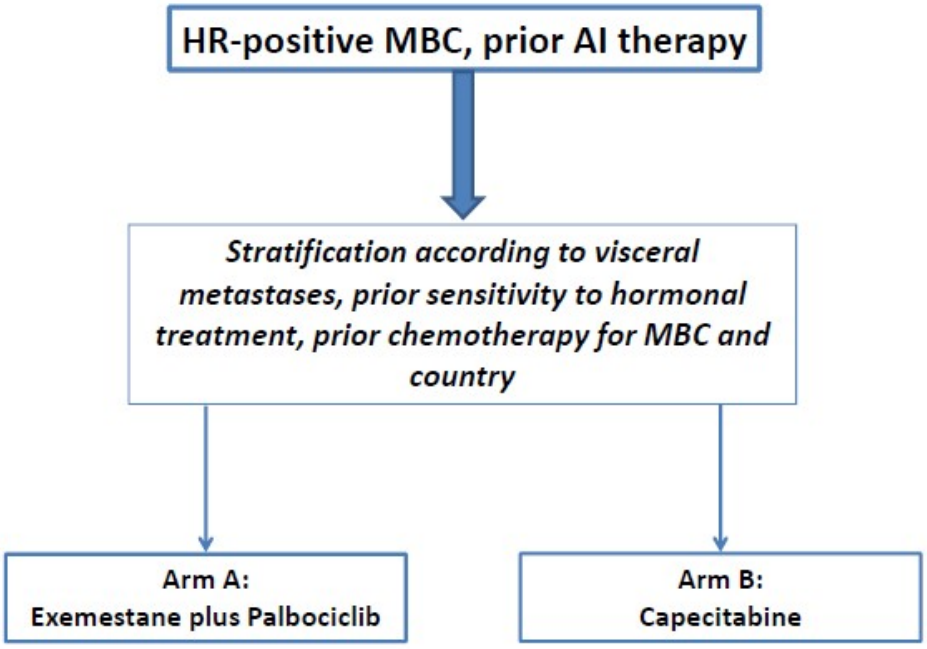
- Approximately 300 patients were to be randomized 1:1 between the experimental arm (Arm A: approximately 150 patients treated with palbociclib plus exemestane) and the control arm (Arm B: approximately 150 patients treated with capecitabine) before the approval of the protocol version 5.0 dated 09Mar2016 (Cohort 1).
- Approximately 300 patients will be randomized 1:1 between the experimental arm (Arm A: approximately 150 patients treated with palbociclib plus fulvestrant) and the control arm (Arm B: approximately 150 patients treated with capecitabine) from the approval of protocol version 5.0 dated 09Mar2016 (Cohort 2).

Patients will be stratified by:

- Site of disease: visceral vs non-visceral (visceral are all lesions not included in the following list: breast, skin, subcutaneous tissue and other soft tissue, lymph node, or bone).
- Prior sensitivity to hormonal treatment:
    - Yes defined as:
        - At least 24 months of endocrine therapy before recurrence in the adjuvant setting in patients who have not received previous endocrine therapy in the metastatic setting.
        - Response or stabilization for at least 24 weeks of the most recent line of endocrine therapy in patients who have received previous endocrine therapy in the metastatic setting.
    - No: all other options

- Prior chemotherapy for MBC: yes (chemotherapy administered as "second adjuvant therapy" for locoregional recurrence should be considered as prior chemotherapy for MBC) vs no.
- Country.

Figure 4. Study Design Cohort 1



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

- ✓ Palbociclib, 125 mg, orally once daily on Day 1 to Day 21 followed by 7 days off treatment on every 28 days cycles;

in combination with

- ✓ Exemestane, 25 mg, orally once daily (continuously).

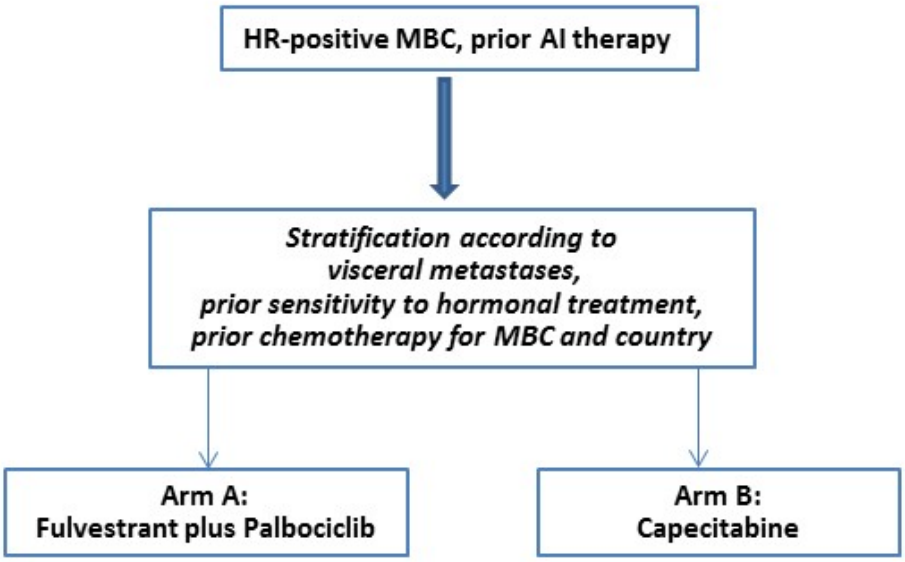
In patients within the PK sub-study, exemestane will be administered daily during a 7-day lead-in period (day minus-7 through day minus-1) immediately preceding cycle 1.

NOTE: The start date of each cycle will be given by the start date of palbociclib intake.

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

- ✓ Capecitabine, 1,250mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000mg/m^2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.

Figure 5. Study Design Cohort 2



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

- ✓ Palbociclib, 125 mg, orally once daily on Day 1 to Day 21 followed by 7 days off treatment given as every 28 days cycles;

in combination with

- ✓ Fulvestrant 500 mg, two 5ml intramuscular injections (one in each buttock) on Days 1 and 15 (±3 days) of Cycle 1, and then on Day 1 of each subsequent 28 days Cycle (± 3 days).

NOTE: The start date of each cycle will be given by the date of administration of the first fulvestrant dose.

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

- ✓ Capecitabine, 1,250mg/m^2 twice daily for 2 weeks followed by a 1 week rest period, given as 3 weeks cycles. Capecitabine must be administered at a dose of 1,000mg/m^2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.

In both Cohorts patients will continue to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurs first. Patients with permanent discontinuation of palbociclib for a reason different than progression (i.e., toxicity due to palbociclib) will continue with exemestane/fulvestrant (in the active treatment phase) until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first. Patients with permanent discontinuation of

exemestane/fulvestrant will be discontinued from the active treatment phase and entered into the follow-up phase.

Disease assessments will be performed at baseline and every 8 weeks (± 7 days) from the start of treatment and every 12 weeks (±7 days) after 120 weeks of treatment. All lesion measurements must be recorded in the eCRF. Disease assessment for all patients at baseline will include:

- ✓ CT scan or MRI of the chest, abdomen and pelvis (CAP). PET-CT scan will be accepted in case the CT scan of this imaging test is meeting with the RECIST version 1.1 requirements for tumour lesion evaluation.
- ✓ Bone scan is mandatory if the patient has bone disease or if there is any suspicious of bone metastases. PET scan will be also accepted to assess the already known or newly suspected bone metastatic disease. Any suspicious abnormalities (ie, hotspots) identified on the bone or PET scan at baseline must be confirmed by X-ray (only if there are other measurable lesions), CT scan with bone windows or MRI (if only bone disease is present).
- ✓ Brain CT scan or MRI is mandatory if the patient has CNS metastases or if there is any suspicious of CNS metastases.
- ✓ CT scan or MRI scan of any other sites of disease as clinically indicated.
- ✓ Clinical assessment of superficial disease by callipers which will include colour photographs of all superficial metastatic lesions including a rule to estimate the size of the lesion. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective.

Patients with bone lesions identified at baseline will repeat the bone scans 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) and to confirm a complete response. The method chosen to confirm the bone metastases at baseline (X-ray, if there are other measurable lesions, CT scan with bone windows or MRI, if only bone disease is present) must follow the same assessment schedule as for measurable lesions, every 8 weeks (± 7 days) from the start of treatment and every 12 weeks (±7 days) after 120 weeks of treatment.

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. While patients are on study therapy, tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow up), whichever occurs first.

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) from the last tumor assessment and bone scans (if applicable) as clinically indicated until RECIST-defined disease progression, initiation of new anticancer 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.

Patients discontinuing the tumor assessments for the primary endpoint will enter a follow up period during which survival and new anti-cancer therapy information will be collected every 6 months (± 14 days) from the last tumor assessment. The follow up period will conclude at the time of the final OS analysis. Crossover will not be allowed in the trial.

3.1.1. Early Safety Review and Pharmacokynetic analysis

The safety of the combination of palbociclib plus exemestane at the recommended doses will be assessed with a limited number of patients exposed to it.

An early safety review was performed which data was evaluated by the Independent Data Monitoring Committee (IDMC). The IDMC made the recommendation to continue the study as planned based on the proportion of grade 4 neutropenia, grade 4 thrombocytopenia or grade 3 QTc prolongations. The Steering Committee (SC) took the decision to accept this recommendation.

PK analysis sub-study of the palbociclib and exemestane combination has been performed. The PK data indicate a lack of a clinically meaningful drug-drug interaction (DDI) between palbociclib and exemestane when both drugs are coadministered (103).

3.2. Duration of the study

The study accrual has been completed in 52 months.

All patients included will receive study therapy until radiographic or symptomatic progression, unacceptable toxicity or withdraw of the informed consent, whatever occurs first.

For safety reasons all patients will have a visit 30 (±5) days after finishing the study treatment. This post-treatment visit must be performed before the initiation of any new anticancer therapy and may be advanced when a new anticancer therapy is scheduled before 30 (±5) days after finishing the study treatment.

After progression all patients will be followed till death or data cut-off date (estimated to be approximately 76 months from the inclusion of the first patient) to evaluate the OS objective.

According to what is outlined above, the length of study will be approximately 6.3 years.

The end date of study is the date of the database lock and it will be independent of performing the analyses of the exploratory objectives.

4. Study Population

4.1. Inclusion Criteria

Patients are eligible to be included in the study only if they **meet all** of the following criteria:

1. The patient has signed the informed consent document.
2. a) *Patients included in Cohort 1*: Females with histologically confirmed MBC whose disease was resistant to previous non-steroidal aromatase inhibitors (letrozole or anastrozole), defined as:
   - ✓ Recurrence while on or within 12 months after the end of adjuvant treatment with a NSAI or
   - ✓ Progression while on or within 1 month after the end of treatment with NSAI for advanced disease.

   b) *Patients included in Cohort 2*: Females with histologically confirmed MBC whose disease was resistant to previous aromatase inhibitors (exemestane, letrozole or anastrozole), defined as:
   - ✓ Recurrence while on or within 12 months after the end of adjuvant treatment with an AI or
   - ✓ Progression while on or within 1 month after the end of treatment with an AI for advanced disease.
3. Previous chemotherapy is permitted either in the (neo)adjuvant setting and/or first line therapy for MBC (chemotherapy administered as "second adjuvant therapy" for locoregional recurrence should be considered as first line chemotherapy for MBC).
4. It is not mandatory to have exemestane, letrozole or anastrozole as the most recent treatment before randomization but recurrence or progression of breast cancer while receiving or after the end of (in the mestastatic setting*immediately* after the end of) the most recent systemic therapy has to be documented before randomization.
5. Hormonal receptor positive (HR+) breast cancer based on local laboratory determination. HR+ defined as ≥ 1% positive cells by IHC for ER and/or PgR.
6. Documented HER2 negative breast cancer based on local laboratory determination on most recent tumor biopsy. HER2 negative tumor is determined according to recommendations of ASCO/CAP 2013 guidelines, as IHC score 0 or 1+ or negative by ISH (FISH/CISH/SISH) defined as a HER2/CEP17 ratio < 2 with an average HER2 copy number <4.0 or for single probe assessment a HER2 copy number < 4.
7. Measurable disease or at least one bone lesion, lytic or mixed (lytic+blastic), which has not been previously irradiated and is assessable by CT/MRI in the absence of measurable disease according to RECIST 1.1 criteria.
8. Patient is at least 18 years of age.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1.
10. Life expectancy ≥ 12 weeks.

11. Adequate organ and marrow function defined as follows:
    - ✓ ANC ≥ 1,500/mm^3 ($1.5x10^9$/L)
    - ✓ Platelets ≥ 100,000/mm^3 ($100x10^9$/L)
    - ✓ Hemoglobin ≥ 9g/dL (90g/L)
    - ✓ Serum creatinine ≤ 1,5xULN and estimated creatinine clearance ≥ 60 mL/min as calculated using the standard method for the institution
    - ✓ Total serum bilirubin ≤ 1,5xULN (≤ 3.0xULN if Gilbert´s disease)
    - ✓ AST and ALT ≤ 3.0xULN (≤5.0xULN if liver metastases present)
    - ✓ Alkaline phosphatase ≤ 2.5xULN (≤5.0xULN if bone or liver metastases present)
12. Postmenopausal women defined as women with:
    - ✓ Prior bilateral surgical oophorectomy, or
    - ✓ Age > 60 years, or
    - ✓ Age < 60 years and medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause or follicle-stimulating hormone (FSH) and estradiol blood levels in their respective postmenopausal ranges.
13. 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).
14. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

4.2. Exclusion Criteria

Patients will be excluded from the study if they **meet any** of the following criteria:

1. Have received more than 1 prior chemotherapy regimen for MBC. (NOTE: Chemotherapy administered as "second adjuvant therapy" for locoregional recurrence should be considered one prior chemotherapy for MBC). Other previous anticancer endocrine treatments for advanced disease are allowed.
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 treatment with any CDK4/6, mTOR or PI3K inhibitor [any agent whose mechanism of action is to inhibit the PI3 kinase-mTOR pathway] or capecitabine.
5. a) Patients included in Cohort 1: Prior treatment with exemestane in the metastatic setting. If the patient has received exemestane in the adjuvant setting and developed MBC, she will be eligible for the study provided:
   - ✓ She has received letrozole/anastrozole as first-line MBC and progressed.
   - ✓ At least 1 year has elapsed since the end of adjuvant exemestane treatment.

   b) Patients included in Cohort 2: Prior treatment with fulvestrant in the metastatic setting. If the patient has received fulvestrant in the adjuvant setting and developed MBC, she will be eligible for the study provided:
   - ✓ She has received letrozole/anastrozole/exemestane as first-line MBC and progressed.
   - ✓ At least 1 year has elapsed since the end of adjuvant fulvestrant treatment.
6. Patients treated within the last 7 days prior to randomization with:
   - ✓ Food or drugs that are known to be CYP3A4 inhibitors
   - ✓ Drugs that are known to be CYP3A4 inducers
   - ✓ Drugs that are known to prolog the QT interval
7. Patients who received before randomization:
   - ✓ Any investigational agent within 4 weeks.
   - ✓ Chemotherapy within a period of time that is < the cycle length used for that treatment (e.g. < 3 weeks for fluorouracil, doxorubicine, epirubicine or < 1 week for weekly chemotherapy).
   - ✓ Previous endocrine therapy is permitted without any window.
   - ✓ Radiotherapy within 2 weeks (all acute toxic effects must be resolved to NCI CTCAE version 4.0 grade <1, except toxicities not considered a safety risk for the patient at investigator´s discretion) but patients who received prior radiotherapy to >25% of bone marrow are not eligible independent of when it was received.
   - ✓ Major surgery or other anti-cancer therapy not previously specified within 4 weeks, (all acute toxic effects must be resolved to NCI CTCAE version 4.0 grade < 1,

except toxicities not considered a safety risk for the patient at investigator´s discretion).

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 > 480msec, 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. Difficulties to swallow tablets, malabsorption syndrome disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or active inflammatory bowel disease or chronic diarrhea.
13. Known hypersensitivity to palbociclib, capecitabine or to exemestane (only patients of cohort 1) or to fulvestrant (patients of cohort 2) or any of their excipients.
14. Any of the following contraindications for chemotherapy with capecitabine:
    - ✓ Known deficiency or family history of deficiency of dihydropyrimidine dehydrogenase.
    - ✓ Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine.
15. Only for patients in Cohort 2 any of the following contraindications for treatment with fulvestrant:
    - ✓ Bleeding diathesis (i.e., disseminated intravascular coagulation [DIC], clotting factor deficiency) or long-term (>6 months) anticoagulant therapy, other than antiplatelet therapy and low dose coumarin derivatives, provided that the International Normalised Ratio (INR) is less than 1.6.
16. Known human immunodeficiency virus infection.
17. 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.
18. Recent or active suicidal ideation or behavior.

4.3. Discontinuations

4.3.1. Discontinuation of Study Treatment

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the study treatment, but can be allowed to continue in the study in order to provide the follow up data needed for the analysis of the entire population. An exception may be granted if the patient, in the opinion of the investigator, is having benefit from the study treatment. In these cases, the investigator must obtain documented approval from GEICAM which in agreement with the Coordinating Investigator and after confirming that this deviation does not affect patient´s safety may allow the patient to continue to receive the study treatment.

Patients can be discontinued from the study therapy in the following circumstances:

- Patient's own request.
- Unacceptable toxicity as defined in the protocol.
- Tumor progression as defined in the protocol.
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Termination of the study by GEICAM.
- Physician's decision, including need of other anti-cancer therapy, not specified in the protocol.
- If the patient is non-compliant with study procedures.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g. infectious disease) illness.
- All patients will be discontinued from the active treatment phase and entered into the follow-up phase in case of a delay of more than 4 weeks or permanent discontinuation of exemestane/fulvestrant unless there is an obvious clinical benefit per the investigator's medical judgment and after discussion with GEICAM. Patients with a delay of more than 4 weeks or permanent discontinuation of palbociclib for a reason different than progression (i.e., toxicity due to palbociclib) will continue with exemestane/fulvestrant (in the active treatment phase) until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.
- All patients will be discontinued from the active treatment phase and entered into the follow-up phase in case of a delay of more than 3 weeks or permanent discontinuation of

capecitabine unless there is an obvious clinical benefit per the investigator's medical judgment and after discussion with GEICAM.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the study treatment.

All permanent treatment discontinuation should be recorded by the Investigator in the eCRF when considered as confirmed.

4.3.2. Discontinuation of Study Sites

Study Site participation may be discontinued if GEICAM, the investigator or the IRB of the study site judges it necessary for any reason.

4.3.3. Discontinuation of Study

The study may be discontinued by GEICAM if this is medically reasonable and consistent with applicable regulations of Good Clinical Practice (GCP). Stopping the study for medical reasons may be required if patients experienced adverse reactions under the treatment with the study treatment or if new information about the safety or effectiveness of the study treatment justifies it.

5. Treatment

5.1. Treatments Administered

5.1.1. Palbociclib

Palbociclib will be administered at a dose of 125mg PO daily on Day 1 to Day 21 following a 1 week of rest period, given as 4 weeks cycles.

5.1.2. Exemestane

Exemestane will be administered at a dose of 25 mg PO daily (continuously).

5.1.3. Capecitabine

Capecitabine will be administered at a dose of 1,250mg/m^2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles.

Capecitabine must be administered at a dose of 1,000mg/m^2 twice daily for 2 weeks followed by a 1 week of rest period, given as 3 weeks cycles, in patients over 70 years of age.

Capecitabine Dose will be calculated for each patient in mg/m2, it is recommeded to calculate the dose according to the Protocol Attachment 4. The real Body Surface Area (BSA) of the patient determined in the baseline visit will be the reference BSA throughout the study. The BSA and the capecitabine dose will be recalculated in the event that patients experience body weight variations greater than 10% during the treatment period.

5.1.4. Fulvestrant

Fulvestrant will be administered at a dose of 500mg, as two 5ml intramuscular injections (one in each buttock), on days 1 and 15 (±3 days) of Cycle 1, and then on Day 1 of each subsequent 28 days Cycle (± 3 days). Time windows extended to ±7 days after 24 weeks.

5.2. Materials and Supplies

The definition of Investigational Medicinal Product [IMP] is a drug that is being studied or used as a reference, even as placebo, in the context of a clinical trial, regardless of its authorization.

All IMPs used in the trial will be named as study treatment along the protocol.

GEICAM will provide the study sites with palbociclib, exemestane and fulvestrant with the appropriate label for clinical trial use for the purpose of this study.

Since capecitabine is a marketed product approved for this indication and is administered according to the label it will not be provided by the Sponsor.

5.2.1. Storage, preparation and administration

Investigators and site staff are reminded to continuously monitor room and fridge storage temperatures and ensure that thermometers are working correctly as required for proper storage of study treatment. These include thermometers for both the room storage and refrigerator storage.

For palbociclib, exemestane and fulvestrant provided by the sponsor, any temperature excursions must be reported immediately to GEICAM and documented. Once a deviation is identified, the study treatment MUST be quarantined and not used until GEICAM provides documentation of permission to use the study treatment product.

Palbociclib, exemestane and fulvestrant should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned study treatment provided by the Sponsor should be stored separately from study treatment that needs to be dispensed.

Refer to the current capecitabine SmPC for details regarding the storage and handling of capecitabine. Any issue or deviation that affect the storage conditions or handling of capecitabine must be reported to the sponsor for its information.

Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

5.2.1.1. Palbociclib

Palbociclib will be supplied as capsules containing 75mg, 100mg or 125mg equivalents of palbociclib free base. GEICAM will supply the oral drug formulation to sites in HDPE bottles containing 75mg, 100mg or 125mg capsules. The capsules can be differentiated by their size and color (see Table 4).

Table 4. Palbociclib Capsule Characteristics

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

Palbociclib will be provided in non-patient-specific bottles containing 75mg, 100mg or 125mg capsules.

Storage conditions stated in the Study Reference Safety Document may be superseded by the label storage.

Palbociclib capsules should be stored at controlled room temperature (15-30ºC) in their original container.

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 guidelines 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.

Palbociclib 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.

Patients should be instructed to swallow palbociclib 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 treatment in a patient diary.

In Cohort 1 palbociclib will be administered together with exemestane. In both Cohorts patients should take palbociclib with food. Palbociclib will be administered orally once a day for 21 days of every 28-day cycle followed by 7 days off treatment.

Patients experiencing investigational product related toxicity may have their dose modified according to Section 5.4.1.

For both palbociclib and exemestane:

- ✓ Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.
- ✓ Patients who vomit any time 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 5.5. for further details on medication errors and overdose.

5.2.1.2. Exemestane

Commercially available exemestane 25mg coated tablets will be supplied to sites by GEICAM. Complete information about exemestane formulation and storage conditions can be found in the Summary of Product Characteristics (SPC) for Aromasin®.

Exemestane tablets will be provided in blister packs.

Exemestane will be administered orally in a daily basis and continuously (together with palbociclib for the first 3 weeks and in monotherapy for the fourth week in 28-days cycles).

5.2.1.3. Capecitabine

Investigators should consult the locally approved prescribing information for storage and administration instructions.

5.2.1.4. Fulvestrant

Fulvestrant (Faslodex®) is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250mg/5mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure. The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlideTM) for connection to the barrel.

Refer to the Summary of Product Characteristics (SmPC) for fulvestrant (Faslodex®) for storage conditions and instructions and steps necessary for drug preparation and administration. Drug preparation and administration will be performed at the site by a physician, registered nurse or other qualified health care provider.

Fulvestrant 500mg will be administered intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5mL injections, one in each buttock.

5.2.2. Accountability

It is the responsibility of the investigator to ensure that a current record of palbociclib, exemestane and fulvestrant disposition is maintained at each study site where study treatment provided by the Sponsor are inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

GEICAM will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

Palbociclib, exemestane and fulvestrant provided by the Sponsor will be preferably destroyed at each participating site. The site must obtain written authorization from the Sponsor before they are destroyed, and this destruction must be documented on the appropriate form.

It is also the responsibility of the investigator to ensure that current records of capecitabine dispensations are available to assure traceability.

5.3. Method of Assigning a Patient to a Treatment

All patients who meet all criteria for enrollment will be randomized to receive palbociclib in combination with endocrine therapy (exemestane or fulvestrant) versus chemotherapy with capecitabine.

All patients will be screened by one of the investigators prior to entry on this study. An explanation of the study and discussion of the expected side effects and presentation of the

informed consent document will take place. Eligible and consenting patients (entered) will be enrolled into the study. In selected sites, patients enrolled in Cohort 1 were offered the participation in the PK study in the experimental arm.

No patients can receive protocol treatment until registration with GEICAM has taken place. All eligibility criteria must be met at the time of registration. There will be no exceptions. Any question should be addressed with GEICAM prior to registration. The eligibility checklist must be completed and signed by the Principal Investigator or Sub-Investigator before enrolling each patient to confirm all inclusion/exclusion criteria and stratifications factors. This eligibility checklist should be filed with the study documentation. Once the eligibility checklist is completed, the study personnel at the site will randomize the patient through the eCRF and the system will send the unique randomization number of the patient and the assigned treatment to the site.

Only after the assigned arm has been confirmed the patient can receive the study treatment.

All patients enrolled in the study will be registered in a *Patient Enrollment and Identification Log* that will be only maintened at the site.

Trial treatment must be administered within 7 days from registration.

5.4. Special Treatment Considerations. Dose Adjustments of Study Treatment

All dose modifications should be based on the worst preceding toxicity.

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 treatment may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, dosing adjustments may be required for just one or both study treatment in the combination. In the event treatment interruption is deemed necessary for just palbociclib, treatment with the other study treatment (exemestane or fulvestrant) will continue as planned.

For patients in Cohort 1, dose modifications of any nature must not alter the pre-planned schedule of cycles starting with the first palbociclib dose on cycle 1, day 1.

For patients in Cohort 2, if there is dose delay of palbociclib, the administration of fulvestrant should be continued as pre-planned schedule, though every effort should be made to re-synchronize the day 1 palbociclib administration and fulvestrant injection using the allowed visit windows as defined in the study schedule. Fulvestrant can also be delayed by a maximum of 7 days, or longer if required for satisfactory recovery of the platelet count (see Protocol Attachment 6. Fulvestrant/Palbociclib Interruptions and Extended Rest Periods).

All dose modifications/adjustments must be clearly documented in the patient's source notes and the appropriate section of the eCRF.

5.4.1. Palbociclib

In the event of significant treatment-related toxicity, palbociclib dosing may be interrupted or delayed and/or reduced as described below. 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 palbociclib treatment permanently due to treatment-related toxicity will continue with exemestane/fulvestrant (in the active treatment phase) until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

5.4.1.1. Dosing Interruption

Patients experiencing the following adverse events must interrupt/delay their treatment:

- ✓ Grade 3-4 anemia (<8 g/dL; transfusion indicated and/or Life-threatening consequences);
- ✓ Grade 3-4 neutropenia (ANC<1,000/mm^3) either complicated or not;
- ✓ Grade 3-4 thrombocytopenia (Platelet count <50,000/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).
- ✓ Concurrent ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN.
- ✓ Interstitial Lung Disease (ILD)/pneumonitis of any grade. In patients who have new or worsening respiratory symptoms (e.g. hypoxia, cough, dyspneoa, etc) and are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient.

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 5.4.1.2.

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 5.4.1.3. unless expressly agreed otherwise following discussion between the investigator and GEICAM. 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 >4 weeks, treatment resumption will be decided in consultation with GEICAM.

In the event that the start of a new cycle is delayed, procedures required on Day 1 of the given cycle will be performed when treatment is resumed. New cycle Day 1 procedures (ie. physical examination, ECOG performance status, 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 treatment may be resumed and (2) if performed within 7 days prior to study treatment resumption.

5.4.1.2. Re-treatment criteria

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:

- ✓ Hemoglobin > 8g/dL
- ✓ Platelet count ≥ 50,000/mm^3;
- ✓ ANC ≥ 1,000/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 for 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.
- ✓ Patients who experience concurrent ALT>3xULN and total bilirubin ≥2xULN suspected to be treatment-related (Hy´s law) should be permanently discontinued from the study.

- ✓ Patients who experience Grade ≥3 of ILD/pneumonitis should be permanently discontinued from palbociclib. If < Grade 3, symptomatic treatment could be given and maintain the same dose, or reduce the dose, as per investigator's judgment, taking into consideration the clinical situation of the patient, whether the patient has prior respiratory pathology or not, and the benefit obtained with the study treatment.

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 4 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Section 5.4.1.3. for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 4 weeks of dose interruption (including the scheduled 1 week off treatment) or 4 weeks of cycle delay, permanent discontinuation of palbociclib treatment should be considered. Treatment resumption for patients recovering from treatment-related toxicity after > 4 weeks of treatment interruption or cycle delay, but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment, should be discussed with GEICAM.

5.4.1.3. Dose Reductions

Following dose interruption or cycle delay the palbociclib 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 palbociclib by 1 and, if needed, 2 dose levels (Table 5) will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from palbociclib treatment and will continue with exemestane/fulvestrant in the active treatment phase. In exceptional cases a break on day 10-12 or a prolonged holiday of up to 2 weeks after 2 weeks of treatment are further options to modify dose according to tolerability (if in investigator judgment such schedule is manageable and preferred). This should be previously discussed with GEICAM. All dose modifications/adjustments must be clearly documented in the patient's source notes and Investigational product administration eCRF.

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 5. Available Dose Levels

Dose Level	Palbociclib for 3 out of 4 weeks (3/1 schedule)
Starting dose	125mg/d

-1	100mg/d
-2*	75mg/d
Discontinue Study Treatment or consider 75mg/d 2/2 schedule	

*Palbociclib dose de-escalation below 75mg/d is not allowed. The schedule may move to 75mg/day two weeks on followed by two weeks off after discussion with GEICAM.

Palbociclib mandatory dose modifications for treatment related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 6.

Table 6. Palbociclib Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment.

Toxicity	Restart palbociclib Treatment at:
Grade 3 anemia *(<8 g/dL, transfusion indicated*)	Same dose level*
Uncomplicated Grade 3 neutropenia *(ANC<1000/mm^3)*	Same dose level*
Grade 3 neutropenia *(ANC<1,000/mm^3)* **associated with a documented infection or fever ≥38.3°C with a single measure, or ≥38ºC sustained for more than one hour**	↓ 1 Dose Level
Grade 3 thrombocytopenia *(Platelet count <50,000/mm^3)*	Same dose level*
Grade 4 anemia *(Life-threatening consequences)*	↓ 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
Grade < 3 ILD/pneumonitis	Same dose level or ↓ 1 dose level as per investigator's judgment
Grade ≥ 3 ILD/pneumonitis	Permanently discontinue

* If there is significant delay of recovery to grade 2 (≥7 days in addition to the 1 week off) or repeated grade 3, reduce one dose level.

QTc prolongation management

In the event of QTc prolongation, any 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).

Mandatory dose modifications in the event of QTc prolongation are provided in Table 7.

Table 7. Palbociclib 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 same dose level (1)	Treat reversible cause Withhold treatment until QTc<501 msec Resume treatment at the same dose level. Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec.	Discontinue treatment permanently
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the same dose level (1)	Withhold treatment until QTc<501 msec Resume treatment at the next lower dose level (2) Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec.	Discontinue treatment permanently

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 GEICAM, taking into account the emerging safety data from palbociclib 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 GEICAM in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.

5.4.2. Exemestane

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

Patients discontinuing exemestane treatment due to treatment-related toxicity will be discontinued from the active treatment phase of the study (discontinuing also palbociclib) and entered into the follow-up phase.

5.4.3. Fulvestrant

No dose adjustment for fulvestrant is permitted. A single fulvestrant dose can be skipped a single time in case of a fulvestrant-related toxicity. Treatment delay for fulvestrant-related toxicities will be performed as per the investigator's best medical judgment, but by no more than 7 days.

In the event of a toxicity requiring dosing delay of palbociclib, the administration of fulvestrant should be continued as pre-planned schedule, though every effort should be made to re-synchronize the day 1 palbociclib administration and fulvestrant injection using the allowed visit windows as defined in the study schedule. Fulvestrant can also be delayed by a maximum of 7 days, or longer if required for satisfactory recovery of the platelet count, as it should not be administered if the platelet count is $<50{,}000/mm^3$ (see Protocol Attachment 6. Fulvestrant/Palbociclib Interruptions and Extended Rest Periods).

Patients discontinuing fulvestrant permanently due to treatment-related toxicity will be discontinued from the active treatment phase of the study (discontinuing also palbociclib) and entered into the follow-up phase.

5.4.4. Capecitabine

Toxicity due to capecitabine administration may be managed by symptomatic treatment, dose interruption and dose adjustment. Once a patient's capecitabine dose has been reduced, it should not be increased in subsequent treatment cycles. Capecitabine treatment interruptions are regarded as lost treatment days and the planned treatment schedule should be maintained. Missed doses due to treatment interruptions should not be replaced. Further, if a rest period is extended beyond the beginning of the next scheduled treatment cycle, the complete 14-day capecitabine dosing should be administered when capecitabine treatment is re-initiated and the study treatment schedule should be maintained (see Protocol Attachment 5. Capecitabine Interruptions and Extended Rest Periods).

The patient may begin a new 3-week treatment cycle if the absolute neutrophil count (ANC) is $\geq 1.5x10^9/L$, the platelet count is $\geq 75x10^9/L$ and she has recovered from non-haematologic

toxicity to baseline or grade ≤ 1 and then start treatment with doses indicated below. Otherwise, treatment will be delayed until recovery. If recovery has not occurred after a delay of 3 weeks, then the patient should discontinue from the active treatment phase of the study and entered into the follow-up phase, unless there is an obvious clinical benefit per the investigator's medical judgment and after discussion with GEICAM.

In the event that the start of a new cycle is delayed, procedures required on Day 1 of the given cycle will be performed when capecitabine is resumed. New cycle Day 1 procedures (ie. physical examination, ECOG performance status, 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 treatment may be resumed and (2) if performed within 7 days prior to study treatment resumption.

5.4.4.1. Hematological Toxicity

Guidelines for capecitabine dose modifications due to hematological toxicities are shown in Table 8, Table 9 and Table 10.

Dose reduction of capecitabine is not required unless the ANC is $<1.0x10^9$/L, or the platelet count is $<50x10^9$/L. In addition, no dose reductions or interruptions will be required for anemia (non-hemolytic) as it can be satisfactorily managed by transfusions.

Table 8. Dose Modifications for Neutropenia

Neutrophil Count (ANC)	**Grade 2** *≥1.0 - <1.5 x10^9/L*	**Grade 3** *≥0.5 - <1.0 x10^9/L*	**Grade 4** *< 0.5 x10^9/L*
<u>Laboratory value at start of a treatment cycle</u>: delay treatment start until ANC ≥ 1.5x10^9/L, platelets ≥ 75x10^9/L, and recovery from non-haematologic toxicity to baseline or grade ≤ 1, then start treatment with doses indicated below			
1st occurrence	No dose adjustment	capecitabine 75% of the current dose*	capecitabine 50% of the current dose*
2nd occurrence	No dose adjustment	capecitabine 75% of the current dose*	Discontinue treatment permanently
3rd occurrence	No dose adjustment	Discontinue treatment permanently unless the Investigator considers it is in the best interest of the patient to continue with capecitabine at 50% of the current dose once toxicity has resolved to grade 0-1*.	Not applicable

* It is recommeded to calculate the dose according to the Protocol Attachment 4 by using the current value of the BSA. Dose adjustment > 50% of the initial dose for capecitabine should be previously discussed with GEICAM.

Table 9. Dose Modifications for Thrombocytopenia

Platelet Count	**Grade 2** *≥ 50 - < 75 x10^9/L*	**Grade 3** *≥ 25 - < 50 x10^9/L*	**Grade 4** *< 25 x10^9/L*
Laboratory value at start of a treatment cycle: delay treatment start until ANC ≥ 1.5x10^9/L, platelets ≥ 75x10^9/L, and recovery from non-haematologic toxicity to baseline or grade ≤ 1, then start treatment with doses indicated below			
1st occurrence	No dose adjustment	capecitabine 75% of the current dose*	capecitabine 50% of the current dose*
2nd occurrence	No dose adjustment	capecitabine 75% of the current dose*	Discontinue treatment permanently
3rd occurrence	No dose adjustment	capecitabine 50% of the current dose*	Not applicable

* It is recommeded to calculate the dose according to the Protocol Attachment 4, by using the current value of the BSA. Dose adjustment > 50% of the initial dose for capecitabine should be previously discussed with GEICAM.

In case of certain hematological toxicities, the administration of capecitabine must be interrupted during a treatment cycle, and the doses of capecitabine must be reduced as follows in the present and subsequent treatment cycles (see Table 10).

Table 10. Dose Modification Guidelines for Hematological toxicities within a Treatment Cycle

Toxicity	**Capecitabine**
Grade 4 neutropenia for more than 5 days	50% of the current dose of capecitabine***
Grade 4 thrombocytopenia	50% of the current dose of capecitabine***
Grade 3 febrile neutropenia* (ANC < 1.0, fever ≥ 38.3ºC with a single measure, or ≥ 38ºC sustained for more than 1 hour)	75% of the current dose of capecitabine***

Grade 4 febrile neutropenia (ANC < 1.0, fever ≥ 38.3ºC with a single measure, or ≥ 38ºC sustained for more than 1 hour, and life- threatening sepsis)	Discontinue capecitabine treatment permanently unless the Investigator considers it is in the best interest of the patient to continue with capecitabine at 50% of the current dose once toxicity has resolved to grade 0-1**.

* On second occurrence of grade 3 febrile neutropenia, discontinue capecitabine treatment permanently unless it is in the best interest of the patient to treat with capecitabine at 50% of current dose.
** If the decision has been to continue, on second occurrence of grade 4 febrile neutropenia, discontinue capecitabine treatment permanently.
***It is recommeded to calculate the dose according to the Protocol Attachment 4, by using the current value of the BSA. Dose adjustment > 50% of the initial dose for capecitabine should be previously discussed with GEICAM.

5.4.4.2. Non-Hematological Toxicity

For toxicities which are considered by the Investigator unlikely to develop into serious or life–threatening events (e.g. alopecia, altered taste etc.), treatment will be continued at the same dose without reduction or interruption. If any grade 1 toxicity or any grade of alopecia occurs, treatment will be continued at the initial dose without interruption.

Guidelines for capecitabine dose modifications due to non-hematological toxicity are described in general in Table 11 with additional instructions provided below.

Table 11. General Capecitabine Dose Modification Guidelines for Non-Hematological Toxicity

	Grade 2 and 3	**Grade 4**
Laboratory value at start of a treatment cycle: delay treatment start until ANC ≥ $1.5x10^9$/L, platelets ≥ $75x10^9$/L, and recovery from non-haematologic toxicity to baseline or grade ≤ 1, then start treatment with doses indicated below		
1st occurrence	Interrupt treatment until recovery to grade 0-1, continue capecitabine at 75% of the current dose* with prophylaxis where possible.	Discontinue capecitabine treatment permanently- unless Investigator considers it to be in the best interest of the patient to continue at 50% of the current dose* for capecitabine
2nd occurrence	Interrupt treatment until recovery to grade 0-1, continue capecitabine at 75% of the current dose*.	Not applicable
3rd occurrence	Discontinue capecitabine treatment permanently- unless Investigator considers it is in the best interest of the	Not applicable

	Grade 2 and 3	Grade 4
Laboratory value at start of a treatment cycle: delay treatment start until ANC ≥ $1.5x10^9$/L, platelets ≥ $75x10^9$/L, and recovery from non-haematologic toxicity to baseline or grade ≤ 1, then start treatment with doses indicated below		
	patient to continue on capecitabine treatment at 75% of the current dose*, this dose adjustment should be discussed previously with GEICAM.	

*Dose adjustment > 50% of the initial dose for capecitabine should be previously discussed with GEICAM.

If the **creatinine clearance** decreases during treatment to a value <30 ml/min, capecitabine must be permanently discontinued.

If grade >2 **cardiotoxicity** occurs which is attributable to capecitabine, then capecitabine must be permanently discontinued.

Diarrhea: Capecitabine can induce diarrhea, which can sometimes be severe. In patients receiving capecitabine, the median time to first occurrence of grade 2-4 diarrhea is 31 days, and median duration of grade 3 or 4 diarrhea is 4.5 days. Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. If grade 2, 3 or 4 diarrhea occurs, administration of capecitabine must be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1. Following grade 2 or higher diarrhea, subsequent doses of capecitabine must be decreased (see Table 12). Standard anti-diarrhea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Capecitabine cannot be re-started until diarrhea has resolved to grade 0–1 with the last loperamide dose given at least 24 hours beforehand.

Table 12. Capecitabine Dose Modification Guidelines for Diarrhea

	Grade 2	Grade 3	Grade 4
1st occurrence	Interrupt capecitabine until recovery to grade 0-1, continue capecitabine at 75% of the current dose with prophylaxis where possible.	Interrupt capecitabine until recovery to grade 0-1, then continue at 75% of the current dose	Permanently discontinue capecitabine.
2nd occurrence	Interrupt capecitabine until recovery to grade 0-1, then continue with the current dose	Interrupt capecitabine until recovery to grade 0-1, then continue at 75% of the current dose*	Not applicable

	Grade 2	Grade 3	Grade 4
3rd occurrence	Interrupt capecitabine until recovery to grade 0-1, then continue at 75% of the current dose*.	Discontinue capecitabine permanently.	Not applicable
4th occurrence	Discontinue capecitabine permanently.	Not applicable	Not applicable

* Dose adjustment > 50% of the initial dose for capecitabine should be previously discussed with GEICAM.

Grade ≥ 2 Nausea/Vomiting: For nausea and vomiting, patients must be supplied with anti-emetics in order to self-medicate in case nausea or vomiting occurs at home. The administration of metoclopramide +/- 5-HT3 antagonists is recommended for capecitabine-induced nausea. Adequate secondary therapeutic and prophylactic treatment has to be initiated once nausea or vomiting has occurred. If the nausea or vomiting recurs despite adequate prophylaxis, then dose modifications must also be made according to Table 11 above.

Grade 2/3 Stomatitis: If grade 2/3 stomatitis occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. The stomatitis should be treated symptomatically. Subsequent doses of capecitabine must be administered as in Table 11.

Grade 2/3 Hand-Foot Syndrome: Hand-foot syndrome (palmar-plantar erythrodysesthesia) is a cutaneous toxicity. If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to ≤ grade 1. Subsequent doses of capecitabine must be decreased and administered as per Table 11. Hand-foot syndrome should be treated symptomatically (i.e. use of emollients and/or vitamin E is recommended). The use of vitamin B6 pyridoxine (50 to 150 mg BID) has been reported to be of possible benefit and is permitted for symptomatic or secondary prophylactic treatment of hand-foot syndrome.

Hepatic Insufficiency: In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when capecitabine is administered but no dose reduction is necessary. The effect of severe hepatic dysfunction on capecitabine is not known.

Hyperbilirubinemia and transaminase elevation: Administration of capecitabine must be interrupted if treatment-related elevations in bilirubin of >3.0xULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5xULN occur. Treatment may be resumed when bilirubin decreases to <3.0xULN and hepatic aminotransferases decrease to <2.5xULN.

5.5. Medication Errors and Overdose

Medication errors may result in this study from the administration or consumption of the wrong drug, 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 adverse event (AE) page of the eCRFs and on the SAE form when appropriate. In the event of medication dosing error, GEICAM 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 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 and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) eCRF page (refer to Management, Timing and Assessment of Adverse Events section for further details).

5.6. General Concomitant Medication and Supportive Care Guidelines

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 30 days following the last dose of investigational product and the reason for their administration must be recorded on the eCRF.

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.

5.6.1. Prohibited Medications

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

- ✓ **Anticancer agents:** No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than exemestane 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.

- ✓ **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.
- ✓ **Any concurrent radiotherapy** (except palliative radiotherapy as specified under Section 5.6.3.) is prohibited throughout the duration of the active treatment phase of the study. Patients requiring this procedure will be discontinued from the active treatment phase and will enter the follow-up phase. This radiotherapy will be considered an alternative cancer therapy and will result in censoring the patient for the PFS endpoint.

In addition and only in patients randomized to arm A (Cohort 1 and Cohort 2):

- ✓ **Strong CYP3A inhibitors/inducers:** palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro data indicate that CYP3A and sulfotransferase (SULT) enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Coadministration of a strong CYP3A inhibitor (itraconazole) increased the AUC of palbociclib in healthy subjects by 87%. Based on that, the concomitant use of strong CYP3A inhibitors (e.g., amprenavir, atazanavir, boceprevir, conivaptan, delavirdine, diltiazem, erythromicyn, fosamprenavir, mibefradil, miconazole, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole) and grapefruit or grapefruit juice are prohibited. Coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85%. Based on that, the concomitant use of strong CYP3A inducers (such as phenobarbital, rifampin, phenytoin, rifampicin, carbamazepine, rifabutin, rifapentin, clevidipine, enzalutamide, felbamate, nevirapine, primidone and St. John's Wort) are prohibited.
- ✓ **Drugs known to cause QT interval prolongation** are prohibited during the active treatment phase. Refer to Protocol Attachment 3 for a list of drugs known to predispose to Torsade de Pointes.

In addition and only in patients randomized to arm A (Cohort 2):

- ✓ **Long-term** (>6 months) **anticoagulant therapy** (other than antiplatelet therapy and low dose coumarin derivatives provided that the International Normalised Ratio (INR) is less than 1.6, in this case, if the investigator considers use this therapy it is recommended to place ice in the injection area after the administration of fulvestrant for 5 minutes).

5.6.2. 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 GEICAM is required prior to treatment initiation.

- ✓ **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.

In addition and only in patients randomized to arm A (Cohort 1 and Cohort 2):

- ✓ **Moderate CYP3A Inducers:** Coadministration of moderate CYP3A inducers may also decrease the plasma exposure of palbociclib. Based on that, the concomitant use of moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) is not recommended.
- ✓ **CYP3A Substrates:** PK data are available from a midazolam drug-drug interaction study. Midazolam is a sensitive CYP3A4/5 probe substrate. When midazolam was co-administered with palbociclib, median plasma midazolam concentrations were slightly higher than with midazolam given alone. Coadministration of midazolam with multiple doses of palbociclib increased the midazolam plasma exposure by 61%, in healthy subjects, compared with administration of midazolam alone. This is consistent with a weak time-dependent CYP3A inhibition mediated by palbociclib. The dose of sensitive CYP3A substrates with narrow therapeutic indexes (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced as palbociclib may increase their exposure.
- ✓ **Erythropoietin** should be avoided as it is not indicated for patients under the therapies proposed in this arm and may induce thrombotic events.

In addition and only in patients randomized to arm B:

- ✓ **Proton Pump Inhibitors (PPIs):** Coadministration of PPIs may impair the activity of the oral chemotherapeutic agent capecitabine. Based on that, investigators should be cautious when prescribing PPIs to patients on the capecitabine arm. If needed, alternative antacid therapies may be used including H2-receptor antagonists, and locally acting antacids.

5.6.3. 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 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 patient'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. 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 in arm B at the investigator's discretion for the supportive treatment of anemia.
- ✓ **Anticoagulant treatment**: coumarin derivatives will be permitted if INR is less than 1.6. Those patients on coumarin derivatives with an INR target higher or equal than 1.6 may be switched to low molecular weight heparin (LMWH) if the investigator considers it is on the best interest of the patient, but LMWH should be discontinued 12-24 hours prior to fulvestrant injection and resumed 12-24 hours later and it is recommended to place ice in the injection area after the administration of fulvestrant for 5 minutes).
- ✓ **Palliative radiotherapy** is permitted for the treatment of painful bony lesions or any other metastatic lesions as per investigator's judgment, 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 palbociclib with radiotherapy, palbociclib must be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after. For patients with bone involvement, it is suggested to administer palliative radiotherapy before study initiation if possible and clinically appropriate. (eg, lesions at risk for spontaneous micro-factures or painful lesions). The dates on which palliative radiotherapy is administered should be recorded in concomitant medication.

  Areas that have received palliative radiotherapy cannot be used to assess response to study treatment.
- ✓ Caution is advised on theoretical grounds for any **surgical procedures** during the study. The appropriate interval of time between surgery and palbociclib required to minimize the risk of impaired wound healing and bleeding, if any, has not been determined. Based on the available pharmacokinetic data showing a half-life of 27 hours, palbociclib should be completely washed out within a period of 7 days. Patients should

therefore not have elective surgery within this time period after last intake of palbociclib. Postoperatively, the decision to resume palbociclib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.7. Treatment Compliance

Patients will be required to return all bottles of palbociclib and all blisters of exemestane 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 of palbociclib and exemestane will be documented and recorded.

The patient number should be recorded on the bottle/blister label at time of assignment to a 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 should be returned to the site at the next visit.

Patients included in the control arm (capecitabine) will be given a patient diary and will be asked to return the completed diary at each study visit in order to assess the capecitabine compliance.

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.

Fulvestrant will be administered at the hospital. Its administration will be supervised by the investigator or his/her designee.

6. Efficacy and Safety Evaluations, Sample Collection and Testing (Standard Laboratory Testing) and Appropriateness of Assessments

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule, Protocol Attachment 1.

6.1. Efficacy Assessments

Patients must have at least one demonstrated metastatic lesion at screening to be eligible for inclusion.

All assessments to be performed at baseline and during the study are specified in the Study Schedule, Protocol Attachment 1.

6.1.1. Primary Efficacy Assessments

The primary efficacy variable is PFS based on the investigator's assessment.

PFS is defined as the time from randomization to the first documented progressive disease based on the investigator's assessment, using RECIST version 1.1, or death from any cause, whichever occurs first.

ESR1 mutational status will be determined in circulating free DNA (cDNA) obtained from baseline plasma samples and will be prospectively determined before the interims or final analyses. *ESR1* mutational status will be blinded to the patients, investigators and study team.

6.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments are OR, CB, RD and OS.

- ✓ Overall Survival (OS): is defined as the time from the date of randomization to the date of death from any cause.
- ✓ Objective Response (OR): Tumor response will be assessed based on the investigator's assessment according to the RECIST version 1.1. Tumor assessment will be performed at baseline, the same method of measurement used at baseline will be used for further evaluations, that will be conducted every 8 weeks (±7days). The best response across treatment will be recorded. OR is defined as the complete plus partial responses out of the patients who had measurable disease at baseline.
- ✓ Clinical Benefit (CB): is defined as complete response (CR), partial response (PR), or stable disease (SD) based on the investigator´s assessment lasting more than 24 weeks according to the RECIST version 1.1 in all randomized patients (ITT population)
- ✓ Response Duration (RD): is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documented progressive disease using RECIST version 1.1 and based on the investigator's assessment, or to death due to any cause, whichever occurs first.

6.2. Safety Assessments

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting GEICAM to any event that seems unusual.

The investigator is responsible for appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health-care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

During the course of the study, all patients entering the trial must be evaluated according to the schedule outlined in the flow charts and described below. The results of the evaluation will be recorded in the eCRF pages until the patients are not followed anymore.

6.2.1. Timing of Assessments

All assessments to be performed at baseline and during the study are specified in the Study Schedule, Protocol Attachment 1.

Vital signs assessments will include blood pressure, pulse and body temperature. Baseline standard 12-lead ECG is mandatory to determine the QTc interval; on the other visits they will be only performed if clinically indicated.

The following safety laboratory assessments will be performed by the local laboratories, at the times specified in the Study Schedule:

- Hematology: hemoglobin, WBC, absolute neutrophils, platelet count.
- Blood Chemistry:
  - At baseline visit: fasting glucose, alkaline phosphatase, ALT, AST, total bilirubin, serum creatinine, sodium, potassium, magnesium, total calcium.
  - At treatment visit: fasting glucose, alkaline phosphatase, ALT, AST, total bilirubin, serum creatinine, total calcium

All AEs (and their relatedness to the study treatment) occurring during the study will be documented in the eCRF. AEs will be graded according to NCI-CTCAE version 4.0.

6.2.2. Definitions

The safety definitions are described in the table 13.

Table 13: Safety definitions

Concept	Definition
Adverse Event (AE)	Any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this

	treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. Laboratory abnormalities should be reported as AE only in case they lead to an action on study treatment or if they are serious. Any temporary increase in the severity of a symptom or previous sickness that happens after the baseline of the study is considered also as an adverse event.
Adverse Reaction (AR)	All untoward and unintended responses to a medicinal product related to any dose administered. All expected ARs are listed in the Investigator's Brochure (IB) in case of not authorized investigational product or Summary of Product Characteristics [SmPC] in case of an authorized investigational product. If the nature or the severity of an adverse reaction is not consistent with the applicable product information, the AR is defined as unexpected. The basis for the decision is the current version of the corresponding reference document that has been submitted and approved by the competent authority and the ethics committees. **Accountability criteria** The sponsor will classify the adverse event, based in their causation relation with the investigational product, following the Karch y Lasagna (1977) algorithm, as: o Final: there is reasonable temporal sequence between the drug administration and the existence of the adverse event. This event matches with the adverse reaction described for the investigational product, improves with the omission and reappears after its re-administration and can't be explained by other causes. o Probable: there is reasonable temporal sequence between the investigational product administration and the appearance of the adverse event. This event matches with the adverse reaction described for the drug, improves with the omission and can't be explained by other causes. o Possible: there is reasonable temporal sequence between the investigational product administration and the

	appearance of the adverse event. This event matches with the adverse reaction described for the drug but can be explained by other causes. o Conditional or improbable: there is reasonable temporal sequence between the investigational product administration and the appearance of the adverse event. This event does not matches with the adverse reaction described for the drug and can be explained by other causes. o Not related: there is no reasonable temporal sequence between the investigational product administration and the appearance of the adverse event. This event does not matches with the adverse reaction described for the drug and can be explained by other causes. For expedited reporting purposes it is considered as related the categories: final, probable and possible from Karch y Lasagna (1977) algorithm and as not related the category conditional or improbable of that algorithm. The determination of the possible relation with the study treatment is responsibility of the principal investigator of the site or the person designated by him.
Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)	Any adverse event or adverse reaction that, at any dose: o is fatal (results in death), o initial or prolonged inpatient hospitalization, o a life-threatening experience (that is, immediate risk of dying, defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), o persistent or significant disability/incapacity, o congenital anomaly/birth defect or o an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (eg. medical, surgical) to prevent one of the other serious outcomes listed above.

	Do not confuse the concept "serious", described before, with "severe" which refers to the intensity of the AE or AR (minor/mild/severe). The following events will be considered as AEs of Special Interest (AESIs) and they have to be documented as a SAE and notified to the Pharmacovigilance Department of GEICAM immediately: cancer (except for breast cancer), overdose, misuse and abuse.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any serious adverse reaction whose nature, intensity or consequences do not correspond with the reference information for the investigational product (example, Investigator Brochure [IB] in case of not authorized investigational product or Summary of Product Characteristics [SmPC] in case of an authorized investigational product). The unexpected nature of an adverse reaction is based in the fact of not being observed previously and not in what could be advanced based on the pharmacological properties of the drug.

6.2.3 Management, Timing and Assessment of Adverse Events

AE Classification	Adverse events should be classified following version 4.0 of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI). A copy can be downloaded in the NCI web site: http://evs.nci.nih.gov/ftp1/CTCAE. The investigators team must have access to the CTCAE-NCI version 4.0. The AE not included in the CTCAE will be classified as described on Protocol Attachment 8. The causal relation between the investigational product and the AE will be assessed by the investigator using the Karch y Lasagna (1977) algorithm.
Procedure to notify an AE to GEICAM	The site must notify to GEICAM, through eCRF, the following events: o All adverse events that occur after the signature of the Informed Consent Form. o Preexisting conditions that get worse during the study. o The evaluation of the possible relationship of each

	adverse event to the study treatments or protocol procedure. o The circumstances and data that causes the suspension of the treatment of a patient due to an adverse event. o The events related with progression will not be recorded as adverse events, unless the investigator believes they could have been caused by the study treatments. o The events leading to the clinical outcome of death from disease progression will be included in the efficacy analysis and are not recorded as adverse events, unless the investigator believes they could have been caused by the study treatments.
Timing and assessment of AE (see Protocol Attachment 9)	The site staff will report on the eCRF the information of the AE in the following periods: • **Baseline (after ICD and before study treatments):** study site personnel will note the occurrence and nature of each patient´s medical condition(s) and preexisting conditions in the appropriate section of the eCRF. If a patient never receives study treatments but experiences an adverse event after the ICD is signed, ONLY events the investigator believes may have been caused by a protocol procedure will be reported to GEICAM via eCRF. • **During treatment with the study treatments:** during the study, site personnel will record any change in the condition(s) and the occurrence and nature of any adverse events. A CTCAE grade rating will be assigned before each cycle for any adverse event experienced during the previous cycle. • **30-day (±5 days) post-treatment follow-up period:** each patient will have a 30-day post-treatment follow-up evaluation approximately 30 days following the discontinuation of study treatment and before initiation of new anticancer therapy. Patients should be closely followed for study treatment adverse events in order to detect delayed toxicity. If study treatment-related toxicity is present beyond 30 days post-discontinuation, patients must be followed until the toxicity resolves or improved to baseline, the relationship is reassessed as unrelated, the investigator confirms that no further

	improvement can be expected, another therapy is initiated, or death. • **Long-Term Follow-up Period (after the 30-day (±5 days) post-discontinuation/post-treatment):** only new and ongoing SAEs thought to be related to study treatments or protocol procedures should be documented on the eCRF and immediately reported to GEICAM via the designated transmission method, even if the study has been closed. • **SAES related with study treatment** should be collected and analyzed until they are solved or until the toxicity is considered irreversible.
Reporting of Study Specific AE	In case serum creatinine increase fulfills criteria to be reported as AE, the cause of the renal function impairment should be reported and the renal function impairment should be considered in the grade of the reported AE according to NCI-CTCAE version 4.0. If no cause can be identified and creatinine increase is considered serious or has an action taken on study treatment (dose reduction, dose delay, dose interruption or permanent discontinuation), the "creatinine increase" term should be preferred rather than the "renal failure" term. Any case of renal function impairment should be documented at least by a creatinine value and creatinine clearance. Tests will be repeated until recovery or stabilization and all results will be recorded in the eCRF. Any complementary exams made to explore renal function or the cause of renal failure should be reported in the eCRF and product contrast administration for CT scan should be recorded in concomitant medication.

6.2.4. Management, Timing and Assessment of SAEs

Timing of SAEs (see Protocol Attachment 9)	All the SAEs (either spontaneously or during the trial visits) will be collected since the patient signs the Informed Consent Document (ICD). All the SAEs must be documented in the medical record of the patient and in the eCRF. A follow up of all the SAEs should be done until they are solved or until the toxicity is considered irreversible.

SAEs which do not need to be notified to the Pharmacovigilance Department of GEICAM	The following events are not considered SAEs: o A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event). o Elective surgery planned before signing consent. o Hospitalization which is due solely to a planned study visit and without prolongation. o Routine health assessment requiring admission for baseline/trending of health status (eg. routine colonoscopy). o Medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases. o Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative). o Progression of the malignancy during study (including signs and symptoms of progression), unless the outcome is fatal and death occurred before end of treatment. Thereafter death due to disease progression has not to be reported as SAE. o Hospitalization due to signs and symptoms of disease progression. o An overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background. They will be reported in the eCRF and in the patient record. The rest of SAEs must be notified as described as follows.
Procedure to notify a SAE to the Pharmacovigilance Department of GEICAM	The SAEs must be notified to the Pharmacovigilance Department of GEICAM. A member of the investigator team must complete and sign the GEICAM SAE notification form which will be sent by fax/mail, immediately and always during the 24 hours following knowledge of the SAE:

	Pharmacovigilance Department of GEICAM Fax: +34 917 374 199 farmacovigilancia@geicam.org GEICAM will review the received form and, if necessary, will ask more information to the investigator. When additional information is obtained about the SAEs, or this is solved or is improbable it will change, a follow-up report must be also completed and sent by fax/mail, immediately and always during the following the 24 hours to the Pharmacovigilance Department of GEICAM. If GEICAM suspects that the SAE could be a SUSAR, the investigator should give the follow up information requested. All SAEs/AESIs from the time the patient have the first dose of the study treatments through 30 days following the last administration of study treatments must be reported according to the procedure described below. All SAE regardless of timing must be reported, if considered related to study treatment. Likewise, progression of a patient's underlying condition leading to one of the above should also not be reported as a SAE, but documented as primary study endpoint. GEICAM will report all SAEs and AESIs immediately to the Coordinating Investigator. All SAEs and AESIs will be followed-up by the investigator until satisfactory resolution. Annually all SARs will be reported as the DSUR to the competent authorities and the leading ethics committee, including all SUSARs. Withdrawal from further treatment shall be at the discretion of the investigator.
Adverse Events of Special Interest (AESIs)	For AESIs with immediate notification, GEICAM will be informed immediately (within 24 hours following knowledge of the event), as per the SAE notification instructions, even if not fulfilling a seriousness criterion. An overdose (accidental or intentional) with the study treatments is an event suspected by the investigator or spontaneously notified by the patient and defined as: ✓ The intake of more than 23 capsules of palbociclib during a cycle (e.g. more than two capsules on more than two days of a cycle, more than two capsules during

	the week of break) or more than 2 capsules on the same day. ✓ The intake of more than two tablets of exemestane in the same day on more than three days of a cycle. ✓ The intake of an amount of capecitabine that is 10% higher than is normally used for a given cycle. It has to be reported within one working day as an SAE on an SAE form.
Reporting of AESIs without immediate notification	A non-relevant overdose (accidental or intentional) with the study treatments is an event suspected by the investigator or spontaneously notified by the patient and defined as: ✓ The intake of 22 or 23 capsules of palbociclib in the same cycle. ✓ The intake of 29 or 30 capsules of exemestane in the same cycle when the next cycle has not been delayed. ✓ The intake of an amount of capecitabine that is less than 10% higher than is normally used for a given cycle. It is to be reported to the sponsor in the eCRF.
Reporting of Potential Cases of Drug-Induced Liver Injury	Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin 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 ≥ 3 X ULN concurrent with a total bilirubin ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤ 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 ≥ 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 increased by one time above the baseline value. 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. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, 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 subject, 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 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.
Death on Study	Any death occurring during the active treatment part of the study and within 30 days following the last treatment must be reported to GEICAM as the sponsor within 24 hours, regardless of the relation to study treatment(s), and has to be reported on the death report form section of the eCRF. The cause of death should be documented (cancer-related, treatment-related, cancer- and treatment-unrelated). Autopsy

	reports should be collected whenever possible and sent to GEICAM. Deaths that occur due to tumor progression do not have to be reported as a SAE unless they occurred before end of treatment. Deaths after the end of study which are considered to be related to study treatment have to be reported as SAEs. To the extent feasible sufficient information including relevant laboratory values, ECG, scan, biopsy or autopsy results must be provided by the investigator in the SAE narrative (even if investigator determines the SAE is not related) so as to permit an independent causality assessment by a Competent Authority.

6.2.5. Management, Timing and Assessment of SUSARs

Expedited Notification of SUSAR to the Competent Authorities/IRB	The Pharmacovigilance Department of GEICAM or its designee is responsible to notify to each of the competent authorities and IRBs of the participating countries, all the SUSARs collected in the study, following the procedures shown in the current legislation.
Timing of notification	The deadline for reporting a SUSAR shall be 15 calendar days from when GEICAM becomes aware of it. When suspected SUSAR caused the death of the patient or endangered her life, GEICAM will send the information within 7 calendar days from the date on which it becomes aware.
Expedited reporting of other relevant safety information	GEICAM will also notify, expeditiously, all the information that could modify the balance benefit/risk of the investigational product, or determine changes in its administration pattern or in the study performance, such as: o A qualitative change or an increase in the percentage of occurrence of the SAR expected, which are considered clinically significant. o The SUSAR occurring after completion of the study and are reported by the investigator to the sponsor. o New events related to the conduct of a trial or the development of an IMP likely to affect the safety of patients, such as: ✓ SAE that could be related with the study procedure and could modify the conduct of the

	trial. ✓ A significant risk to patients such as lack of efficacy in a drug used to treat a life-threatening illness. ✓ A major safety finding from a newly completed animal study (such as carcinogenicity). ✓ A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country and if this information is known by GEICAM. ✓ Any recommendation of the IDMC that is relevant to the safety of patients (if applicable). This relevant information shall be notified as soon as possible and no later than 15 days after GEICAM becomes aware of it. Additional information will also be notified as quickly as possible.
Development Safety Update Report (DSUR)	The DSUR that includes the SAEs and SUSARs collected during the study will be sent by GEICAM or its designee to the Competent Authorities and EC/IRB at the time established by the current legislation.
Notification to investigators	GEICAM will communicate to the investigators any safety information that may affect the safety of trial patients, as soon as possible. Information on SUSAR occurred during the study will be sent quarterly, in aggregate, in a list along with a brief analysis of the data provided. They will be informed also, throughout the entire study, of any safety aspect that impacts the performance on the clinical trial or in the product development, including the interruption or modification in the development program of the protocol safety-related.

6.3. Other Assessments

6.3.1. Pharmacokinetic Assessments

These studies will be performed in patients randomized in the experimental arm (palbociclib plus exemestane) of Cohort 1 in selected sites and only in patients accepting to participate.

Enrollment of these patients were to be finalised at the completion of cohort 1 recruitment, samples from approximately 20 evaluable patients were to be collected.

The potential for a clinically significant drug-drug interaction (DDI) between palbociclib and exemestane is considered to be very low. Exemestane is metabolized by cytochrome P 450 3A4 (CYP 3A4) and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1, and 3A4. Therefore, exemestane is unlikely to affect palbociclib PK. Rifampin reduced exemestane exposure by ~50%. However, in a clinical pharmacokinetic study, coadministration of ketoconazole, a potent inhibitor of CYP 3A4, has no significant effect on exemestane pharmacokinetics. Therefore, it is unlikely that palbociclib, which has been shown to be a weak time-dependent inhibitor of CYP3A, will have an effect on exemestane PK.

All efforts are made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time AND collected prior to administration of the investigational product on that day will be considered protocol compliant (ie, a 24 hour post-dose trough sample taken within ± 2 hours 24 minutes of the 24 hour nominal time will not represent a protocol deviation unless the sample was taken after that days dose of investigational product). Patients are instructed to withhold their daily dose of study treatments on PK sampling days until the pre-dose PK sample and safety assessments (ie hematology, blood chemistry) have been completed. The exact time of the sample collection and the most recent dosing time (the previous and the immediately following doses) will be recorded on the eCRF. The date of any missing doses should also be recorded in the eCRF.

In patients within the PK sub-study, exemestane is dosed daily during a 7-day lead-in period (day minus-7 through day minus-1) immediately preceding cycle 1.

Exemestane 24-hour PK trough samples are drawn pre-dose on day minus-1, cycle 1 day 1 (back-to-back days), and on day 14 in cycles 1 and 2. Palbociclib 24-hour PK trough samples should be drawn pre-dose on day 14 in cycles 1 and 2. Trough samples should be taken approximately 24 hours after the last dose of study treatment. If any of the Day 14 Cycle 1 and 2 pre-dose PK samples is not collected at the protocol-specified visit, then the collection of these samples is allowed to be “made-up” on Days 15 through 21 within the same cycle, or on Days 14 through 21 in a later cycle, provided that no doses of palbociclib or exemestane have been missed during that cycle and providing that the palbociclib dose has not been reduced in that patient.

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

These samples are being analyzed for palbociclib and exemestane. The palbociclib results will be compared to historical controls to assess for major differences in PK. Exemestane results will be compared within each patient for major differences in PK (due to large variability in historical reports). These data will be used to explore the DDI potential between exemestane and palbociclib.

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

6.3.2. Biomarker, Pharmacogenomic and Pharmacodynamic Assessments

Detailed instructions for the collection, handling and shipment of samples are outlined in the Sample Management Manual.

Whole Blood Biospecimens: A whole Blood sample (EDTA tubes for whole blood collection optimized for DNA analysis) will be collected whenever feasible (preferable at baseline or within 7 days prior to the first dose of treatment) to be retained for potential pharmacogenomic/biomarker analyses related to drug response or adverse drug reactions. Genomic and metabolomic variation may help to explain some of the variability in response seen with some drugs among different individuals. Comparing the DNA, RNA, protein, and metabolite 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 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. 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.

Plasma Samples for *ESR1* mutational status and exploratory biomarker analyses: Four blood samples (tubes optimized for plasma collection) will be collected from all patients at: 1) baseline (Cycle 1, Day 1 pre-dose or within the 7 days prior to the first dose of study treatment), 2) Cycle 1 Day 15 (± 3 days), 3) Cycle 2 Day 15 (± 3 days), and 4) at the end of treatment (approximate 30 days after last study dose but always before the initiation of any new anticancer therapy), unless prohibited by local regulations. The baseline sample must be drawn prior to the first dose of study treatment and the samples of Cycle 1 Day 15 (± 3 days) and Cycle 2 Day 15 (± 3 days) prior to the fulvestrant dose in patients included in arm A of Cohort 2. For patients included in the PK sub-study, the baseline plasma sample is collected in cycle 1 on day -7 predose or within 7 days prior to the first exemestane dose, because in these patients exemestane will be administered daily during a 7 day lead-in period (day minus 7 through day minus 1) immediately pre-ceding cycle 1. If a patient ends the study treatment due to a reason different than disease progression, every effort should be made to collect an additional sample upon progression (regardless of the administration of other treatment).

In case that a blood/plasma sample is not drawn by mistake at the protocol scheduled timepoint, it should be asked the sponsor for the convenience of collecting the sample at a later timepoint.

ESR1 mutational status will be determined in circulating free DNA (cDNA) obtained from baseline plasma samples and will be prospectively determined before the interims or final analyses. *ESR1* mutational status will be blinded to the patients, investigators and study team. Most common ER-Ligand Binding Domain (ER-LBD) activating mutations (e.g. c.1138 G>C

(E380Q), c. 1607 T>G (L536R), c. 1610 A>G (Y537C), c. 1613 A>G (D538G), c. 1387 T>C (S463P), c. 1609 T>A (Y537N) and c. 1610 A>C (Y537S) (97) will be analyzed to determine *ESR1* mutational status as positive or wild type.

Correlative plasma samples will be collected for exploratory analyses of circulating free DNA or RNA and their relationship to resistance or sensitivity to treatment with palbociclib (mononuclear cell DNA obtained from whole blood samples will be used as a control). Plasma samples will also be analyzed to explore treatment effects on the expression of specific biomarkers.

Tumor Tissue for Biomarker Assessments: For the purpose of eligibility, documentation of HR-positive and HER2-negative tumor will be performed based on local results utilizing an assay consistent with local standards. Most recent formalin fixed paraffin embedded (FFPE) tumor tissue will be collected for biomarker assessments. Samples will be sent to the sponsor designated central laboratories.

Retrospectively, exploratory tumor tissue biomarkers, including DNA, RNA and protein analytes, will be analyzed to investigate possible associations with resistance/sensitivity to treatment with palbociclib. Biomarkers that will be analyzed will be selected based on their known relevance to mechanisms involved in cell cycle regulation or breast cancer development. Examples of such biomarkers include CCND1 and CDKN2A gene copy number, CDK4 and CDK6 RNA expression, and Ki67, pRb, cyclin E and p16 protein expression. The relationship between centrally assessed biomarkers and resistance/sensitivity to treatment with palbociclib will be reported in an exploratory fashion.

A single biomarker will be nominated as the **primary biomarker** for analysis using data external to the current study. The interaction between the primary biomarker and benefit from palbociclib in terms of prolongation of PFS will be examined in a prospective fashion. All other biomarkers will be examined in an exploratory fashion.

6.3.3 Patient Reported Outcomes

Patient reported outcomes of health-related quality of life will be assessed using the EORTC QLQ-C30 and breast modules (QLQ-BR23) instruments and the EuroQol Health Utilities Index EQ-5D-3L instrument (see attachment 10).

The EORTC-QLQ-C30 is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, cognitive emotional, and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global health/quality of life (QOL) subscale, and six single items assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite, diarrhea, constipation, and the financial impact of cancer). The questionnaire employs 28 4-point Likert scales with responses from “not at all” to “very much” and two 7-point Likert scales for global health and overall QOL. For functional and global QOL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale. For symptom-oriented scales, a higher score represents more severe symptoms.

The EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of two functional scales (body image and sexuality); three symptom subscales (arm/hand, breast, and systemic side effects) and single items covering sexual enjoyment, distress at hair loss, and future perspective.

The EuroQol-5D (EQ-5D) (version 3L) 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.

Patients will complete each instrument within 28 days (±7 days) prior to the first treatment administration, pre-dose on Day 1 (-3 days) of every two cycles starting with Cycle 3 until Day 1 (-3 days) of Cycle 7 (at cycles 3, 5 and 7), thereafter on Day 1 (-3 days) of every three cycles till the end of treatment (at cycles 10, 13, etc) and at the post-treatment visit (30 days ± 5days from the last study treatment dose and/or before the initiation of any new anticancer therapy). Patients who discontinue study treatment for reasons other than radiographically and/or clinically documented PD or initiate a new anticancer therapy will additionally complete these instruments after RECIST-defined disease progression. 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). The instruments will be given to the patient in the appropriate language for the site.

7. Data Quality Assurance

To ensure accurate, complete and reliable data, GEICAM will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instructions on the protocol, the completion of the eCRFs, and study procedures
- make periodic visits to the study site to review study progress, investigator and patient compliance with the clinical trial protocol requirements and any emergent problems
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database
- verify the quality of the data

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide GEICAM, applicable regulatory agencies, and applicable ethical review boards with direct access to original source documents.

7.1. Data Management and Registries file

Data for this study will be recorded via an electronic data capture system using eCRFs. Data will be transcribed by the site from the paper source documents onto the eCRF. In no case the eCRF is to be considered as source data for this trial. The eCRFs must be completed in an electronic Data Base called ORACLE. That electronic Data Base carries out with the regulatory authorities requirements. It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by GEICAM to record (according to GEICAM instructions) all observations and other data pertinent to the clinical investigation. All eCRFs should be completed in their entirety in a neat, to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to GEICAM as soon as they are entered in the eCRF.

The computerized handling of the data by GEICAM when available in the eCRF may generate additional requests to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

8. Sample Size and Statistical Methods

8.1. Determination of Sample Size

8.1.1. Sample Size determination

The primary objectives of this study are to demonstrate that the combination of palbociclib and fulvestrant is superior to capecitabine in prolonging PFS in postmenopausal women with HR+/HER2- metastatic breast cancer, whose tumors are resistant to prior aromatase inhibitors (Cohort 2) and to demonstrate that palbociclib in combination with endocrine therapy (exemestane or fulvestrant) is superior to capecitabine in prolonging PFS in postmenopausal women with HR positive/HER2 negative MBC whose disease was resistant to aromatase inhibitors and whose tumor had estrogen receptor (*ESR1*) mutational status as wild type at study entry (Cohort 1 + Cohort 2). All patients from Cohort 2 and patients with *ESR1* mutational status as wild type from Cohort 1 + Cohort 2 are eligible for the two primary inferential assessments of efficacy.

Cohort 2 will have an 80% power to detect a difference between the control arm with a median PFS of 6 months and the experimental arm (palbociclib plus fulvestrant) with a median PFS of 9 months, for a hazard ratio of 0.667, with a 5% significance level. Assuming a non-uniform accrual accomplished over a period of about 26 months, and a follow-up period for the final PFS analysis of about 28 months from the start of study randomization of Cohort 2, a total sample size of approximately 300 patients (150 in each treatment arm) will be required and the necessary number of events for the final PFS analysis is determined to be 193.

Cohort 1 + Cohort 2 (*ESR1* wild type) should have an approximately 80% power to detect a difference between the control arm with a median PFS of 6 months and the experimental arm (palbociclib plus fulvestrant or exemestane) with a median PFS of 9 months, for a hazard ratio of 0.667, with a 5% significance level in *ESR1* mutation status as wild type patients. The sample size will be similar to Cohort 2. Approximately 308 patients and 193 PFS events will be accumulated if we assume 80% cDNA collection/detect rate and 70% of patients will have tumors with *ESR1* mutational status as wild type at study entry (approximately 140 mutational status as wild type from 250 patients from Cohort 1 and 168 mutational status as wild type from 300 patients from Cohort 2).

The sample size described above will also allow the assessment of differences in the secondary endpoint of overall survival (OS). The median OS for women with advanced or metastatic breast cancer treated with capecitabine is assumed to be 22 months. With an overall significance level of 10% and one interim analysis of OS (at the time of PFS final analysis), Cohort 2 will have approximately 80% power to detect a hazard ratio of 0.667 (representing a 50% increase in median OS from 22 months to 33 months) when approximately 152 deaths have occurred after an approximate follow-up of 50 months from the start of study randomization. Similar sample size determination also applies to Cohort 1 + Cohort 2 (*ESR1* wild type).

8.2. Statistical and Analytical Plans

8.2.1. General Considerations

Statistical analysis of this study will be the responsibility of GEICAM. The interpretation of study results will be the responsibility of the principal investigator of the study.

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 GEICAM. 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.

8.2.1.1. Patient Populations

Intent to treat population (ITT): The ITT population will include all patients who are randomized, with study treatment assignment designated according to initial randomization.

***ESR1* wild type population:** The *ESR1* wild type population will include all patients who are randomized, with study treatment assignment designated according to initial randomization and whose tumor had estrogen receptor (*ESR1*) mutational status as wild type at study entry.

The ITT and *ESR1* wild type populations will be the primary populations for evaluating patient characteristics and efficacy.

Per-protocol population: a subset of the ITT population that received at least one dose of study treatment and completed the study without certain major protocol deviations according to the Appendix I of the Protocol Deviation Manual.

Safety population: will include all patients randomized in the study who received at least one dose of treatment. This population is for the safety analysis.

PK population: a subset of included patients with evaluable PK samples.

Biomarker population: a subset of included patients with available biological samples and clinical data for Biomarker, Pharmacogenomic and/or Pharmacodynamic analysis.

QoL population: a subset of enrolled patients with available QoL questionnaires *(the baseline and at least one more).*

8.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- summary of patients entered and by site
- total number of patients entered
- total number of patients enrolled
- summary of reasons for patients entered, but not enrolled
- total number of patients treated

- summary of reasons for patients enrolled, but not treated.

A detailed summary of reasons for patient discontinuation from study treatment will be provided.

A summary of all identified important protocol deviations will be provided.

8.2.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- patient demographics
- baseline disease characteristics
- preexisting conditions/secondary conditions
- prior therapy

Other patient characteristics will be summarized as deemed appropriate.

Standard descriptive statistics, such as the mean, median, range and proportion, will be used to summarize the patient sample and to estimate parameters of interest. Ninety-five percent confidence intervals will be provided for estimates of interest where possible.

8.2.4. Concomitant Therapy

A summary of concomitant therapies will be generated in the safety population.

8.2.5. Treatment Compliance

Treatment information will be collected at each dose administration. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual dose administered per week}}{\text{Dose expected to be administered per week}} \times 100$$

No minimal level of compliance will be defined for patient inclusion in efficacy analyses. To be considered compliant patients should have received at least 80% of the planned number of doses. Exploratory analysis of the impact of compliance on selected efficacy endpoints may be performed if deemed necessary.

8.2.6. Efficacy Analyses

All efficacy analysis will be based on the ITT and *ESR1* wild type populations. Additional PFS and OS analyses will be performed on the per-protocol population. All analysis will be performed using the SAS Enterprise Guide 5.1 version.

All primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumor burden (PFS, ORR, CBR and RD) will be derived using the local radiologist's/investigator's assessment.

8.2.6.1. Analyses 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 1 day duration. 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.

A modification of Hochberg's method (98) will be used for two primary treatment comparisons to provide control of experiment-wise Type 1 error at a 5% significance level. With this closed testing method, statistical significance applies to both p_1 for Cohort 2 and p_2 for Cohort 1+ Cohort 2 (*ESR1* wild type) if $p_1<0.05$ and $p_2<0.05$; or it applies only to Cohort 2 if $p_1\leq0.025$ when Cohort 1+ Cohort 2 (*ESR1* wild type) has $p_2>0.05$; or it applies to only Cohort 1+ Cohort 2 (*ESR1* wild type) if $p_2\leq0.025$ when Cohort 2 has $p_1>0.05$ (assuming the analyses results represented by both p_1 for Cohort 2 and p_2 for Cohort 1+ Cohort 2 (*ESR1* wild type) demonstrate that the combination of palbociclib and fulvestrant and palbociclib and endocrine therapy respectively are superior to capecitabine in prolonging PFS).

The primary analyses of PFS will be performed in the ITT population for Cohort 2 and *ESR1* wild type population for Cohort 1 + Cohort 2. A stratified log-rank test 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 5%. The stratification factor(s) will be specified in the SAP. PFS time associated with each treatment arm will be summarized for the ITT/*ESR1* wild type population**s** 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. Additionally a similar analysis will be also performed in the per-protocol population**.**

The secondary analysis of PFS will be performed in the ITT population for Cohort 1 + Cohort 2. Statistical methods for this analysis will be the same that outlined above.

8.2.6.2. Analysis of Secondary Endpoints

The secondary efficacy endpoints are:

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.

OS will be analyzed in the ITT population for Cohort 2, *ESR1* wild type population for Cohort 1 + Cohort 2 and ITT population for Cohort 1 + Cohort 2. A stratified log-rank test will be used to compare OS time between the 2 treatment arms at the interim and/or final analyses with the overall significance level preserved at 0.10. The stratification factor(s) will be the same as for

the PFS analysis. 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. Additionally a similar analysis will be also performed in the per-protocol population.

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 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 ITT/*ESR1* wild type patients with measurable disease by treatment arm ("response rate").

$$\text{Objective Response Rate} = \frac{\text{Number of CRs + PRs}}{\text{ITT or ESR1 wild type population with measurable disease}}$$

The ORR will be reported, including a 95% confidence interval. ORR comparison between the two treatment arms will be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis.

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

Response Duration (RD): 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 death due to any cause, whichever occurs first. RD 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. 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.

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

Clinical Benefit (CB): clinical benefit is defined as complete response (CR), partial response (PR), or stable disease (SD) ≥24 weeks according to the RECIST version 1.1, recorded in the time period between randomization and disease progression or death of any cause.

Clinical benefit (CB) rate (CBR) on each randomized treatment arm will be estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the ITT/*ESR1* wild type populations by treatment arm. A 95% CI for the CBR will be provided. CBR comparison between the two treatment arms will be assessed using CMH test with the same stratification factors as for the PFS analysis.

All of the above secondary analyses will be conducted at a two-sided 0.05 level of significance. Additional sensitivity analyses will be outlined in the SAP.

8.2.7. Safety Analyses

The toxicity and tolerability of study treatment will be evaluated in the safety population. Safety analyses will include summaries of the incidence of adverse events by maximum CTCAE grade (v4.0; NCI 2010) that occur during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality and according to the relationship to study treatment as assessed by the investigator. Additionally, the following safety-related outcomes will be summarized:

- study treatment discontinuations due to adverse events.
- deaths
- SAEs
- hospitalizations and transfusions
- use of key concomitant medications or growth factors.

Analyses for data with discrete dates, for example, deaths, transfusions, and concomitant medications, will be done through 30 days after each patient's last dose of study treatment. Adverse events will also be analyzed in this timeframe; that is, if an event starts within 30 days of discontinuation from study treatment, but after 30 days after the last dose of study treatment, it will not be included.

Adverse events data and serious adverse events will be presented in frequency tables by grade. Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. The safety analysis will be performed in the safety population.

An early safety review will be performed by the IDMC. In addition, the interim analyses for PFS will provide the potential to identify early any unexpected safety issues associated with the palbociclib combinations.

8.2.8. Other Analyses

8.2.8.1. Pharmacokinetic Analysis

Within-patient average trough concentrations will be listed by patient by analyte. Summary statistics will be provided for palbociclib trough concentrations by study cycle and for within-patient average trough concentrations. Summary statistics will be provided for exemestane trough concentrations by nominal collection time, for within-patient average trough

concentrations during the exemestane lead-in period, and for the within-patient average trough concentrations from Day 14 of Cycles 1 and 2.

8.2.8.2. Biomarker, Pharmacogenomic and Pharmacodynamic Analysis

For 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. In all possible cases, the 95% confidence intervals will be calculated. If appropriate, a chi-squared test will be used to test group differences for categorical variables.

Appropriate statistical methods will be used to investigate any possible relationship of biomarker levels with palbociclib plus endocrine treatment anti-tumor efficacy.

If applicable, parametric test (analysis of variance or t test) or non-parametric testing, such as Wilcoxon's rank-sum test or Kruskal–Wallis test for continuous variables, and the Pearson $\chi 2$-test or Fisher exact test for categorical variables will be used to test group differences. All test performed will be two-sided and carried out with a 5% α-error rate without correction for multiplicity.

If applicable, the analysis described in this paragraph will be performed.The Kaplan-Meier limit-product method will be used to estimate the primary or secondary efficacy endpoints (PFS, OS, RD, etc.). The comparison of those endpoints between groups will be performed using the Log-Rank test. The Kaplan-Meier survival curves will be presented graphically. Median PFS, OS and RD with the 95% confidence interval will be reported. Cox regression models will be used to estimate unadjusted and adjusted hazard ratio and its 95% confidence interval. The Wald test will be used to establish the prognostic importance of each variable. If needed logistic regression models will be used to test the association of biomarkers with OR and CB and to estimate odds ratios and their 95% confidence intervals. If applicable, univariate and multivariate analyses will be carried out to explore the influence of the selected variables in PFS, OS, RD, ORR, CBR, etc. If appropriate, additional statistical analysis will be performed to investigate any possible relationship of biomarker levels with outcome and/or study treatment efficacy. Any additional sensitivity analyses will be outlined in specific SAPs.

8.2.8.3. Patient Reported Outcomes

Breast cancer-specific quality of life scores and change from baseline scores will be compared between the treatment arms using a mixed model repeated measures 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.

In addition to the above analyses, an examination of the time to deterioration composite endpoint will be carried out using survival analysis methods. A composite definition for

deterioration based on death, tumor progression, and/or breast cancer-specific quality of life subscale MIDs may be used.

8.2.9. Subgroup Analyses

Exploratory subgroup analysis may be performed if deemed appropriate.

8.2.10. Interim Analysis

The study is designed to have two interim analyses and the final analysis based on the primary endpoint of PFS. The first interim analysis will be performed after approximately 150 patients have documented progressive disease or death in Cohort 1 and only patients randomized to Cohort 1 will be included. The enrollment of Cohort 2 will not be affected by the outcome of the first interim analysis. The purposes for the first interim analyses are to assess the safety of the patients and to potentially re-evaluate the assumption of the proportion of patients with ESR1 wild type randomized to the study which may affect the sample size determination for Cohort 1 + Cohort 2 (*ESR1* wild type) analyses. The second interim analysis will be performed on Cohort 2 and Cohort 1 + Cohort 2 (*ESR1* wild type) after approximately 116 patients have documented progressive disease or death in Cohort 2 (approximately 60% of the total events expected for Cohort 2). The purposes for the second interim analyses are to allow for early stopping of the study for efficacy, futility, to assess the safety of the combination regimens and to potentially re-estimate the sample size of the trial. The significance level will be allocated to the second interim and final analyses with a Bonferroni method, such as alpha=0.002 for the second interim analysis and alpha=0.048 for the final analysis. The same Hochberg method described above will be used for the second interim analysis.The rho spending function family (99) will be used for the futility boundary (rho=4, non-binding) for PFS at the second interim analysis. Non-binding for futility implies that the futility boundary will be constructed in such a way that it can be overruled if desired by the IDMC without inflating the Type I error rate. The total Type I error rate will be well preserved. The sample size of the study may be adjusted at the second interim analysis using the method outlined by Cui et al. (100) and applied to the time-to-event endpoint. Using the Cui method guarantees that the overall type I error will still be preserved after a sample size increase. Specific details regarding the efficacy and futility boundaries, and sample size re-adjustment will be described in the SAP. If the results of the interim analyses indicate serious safety concerns, the IDMC will alert the SC with the recommendation to stop the clinical trial for safety reasons.

8.2.11. Data Monitoring Committees

The study will use an IDMC. The IDMC membership and governance is outlined in a separate charter.

The IDMC will be responsible for ongoing monitoring of the efficacy and safety data from patients in the study according to the Charter. The IDMC will make recommendation as to whether or not the trial should continue based on ongoing reviews of safety data. In addition,

the IDMC will also evaluate the interim efficacy data and make a recommendation regarding study continuation based on observed results of the study.

In addition to the use of the IDMC, the safety of the trial will also be monitored by the SC. The recommendations made by the IDMC to alter the conduct of the study will be forwarded to the SC for final decision. GEICAM will designate a biostatistician not affiliated with the project to prepare data for IDMC review. Clinical sites will be restricted from access to study results until the conclusion of the study.

8.2.12. Criteria for End of Study

This study will be considered complete following the data cut-off date and datalock for the final analysis of OS. The data cut-off date for the final analysis will occur when approximately 50% of enrolled patients in Cohort 2 (approximately 152 patients) have died.

If further data are collected that are not included as part of the final locked database, the postlock data will eventually be combined with the locked database and stored in a data library separate from the locked database.

Performing exploratory objectives will be independent of the date of the end of the study.

9. Informed Consent, Confidentiality, Responsibility Insurance and Regulatory Considerations

9.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing any new information that may be relevant to the patient's willingness to continue his or her participation in the trial in a timely manner.

The informed consent document will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study treatment.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. The Coordinating Investigator will assess if all patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

9.2. Respect of Confidentiality

The investigator will be responsible for preserving the suitable information about each patient (for example, name, address, telephone number, social security number and study identification) so that the competent authorities can have access to said information if necessary. These records must be confidentially preserved for the time indicated by the legislation.

The investigators and GEICAM will maintain the confidentiality of all patients participating in the study, according to Good Clinical Practice, GCP and local legislation.

This clinical trial will be held in accordance and in compliance with local current legislation.

9.3. Responsibility Insurance

GEICAM has signed an insurance policy to cover the responsibilities of the investigator and those of other parties participating in the study.

9.4. Regulatory Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. The investigator, head of the medical institution, or designee will promptly submit the protocol to applicable ethical review board(s).

9.4.1. Investigator Information

Physicians with a specialty in medical oncology will participate as investigators in this clinical trial.

If investigators are added after the study has been approved by GEICAM, an EC/IRB, or a regulatory agency, these additions will not be considered changes to the protocol.

9.4.2. Protocol Signatures

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to GEICAM.

10. Practical Considerations

10.1. Monitoring, Audit and Inspections

The study will be monitored by means of regular visits of the patients. During the visits to the center, the monitor must review the original records of the patients, the records of medication stocks and document preservation. The monitor must also evaluate the study procedures and discuss the possible problems with the investigator. During the course of the study, audit visits can be carried out in the participating centers. The investigator will allow direct access to the source documents/data for the tasks of monitoring, audit, reviewed by the EC/IRB and the inspection by the Competent Authorities.

10.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with GEICAM or designee (and IRB or EC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

10.3. Preservation of Study Documentation

The copies of all the relevant information will be preserved by the investigator for a period of at least 25 years after the end of the study, according to current legislation.

10.4. Protocol Modification

Once it has been authorized by the EC/IRB and the competent authority any protocol modification must be documented by writing, in the form of an amendment.

The amendments must be duly identified, by its chronological order number, dated and signed by GEICAM and the Coordinating investigator.

All the protocol amendments must be notified to the EC/IRBs involved in the trial and to the competent authority. If the modifications are relevant, the authorization of the involved EC/IRBs and/or the competent authority will be necessary before their application.

After reading the protocol amendment and prior to the submission to the EC/IRB, each principal investigator will sign the protocol amendment signature page and send a copy of the signed page to GEICAM.

10.5. Use of the Information and Publication

All the information concerning the study treatment provided by GEICAM in relation to this study, and not previously published, is considered to be confidential information with property right of GEICAM. This information comprises the basic information about the product, the clinical protocol, the work forms where appropriate, the e-CRFs, the assessment methods, the technical methodology and the basic scientific data. This confidential information will be the

property of GEICAM, it must not be disclosed to third parties without the prior written consent of GEICAM and it must not be used other than for the purposes of the study.

The information developed during the practice of this clinical study is also considered to be confidential. This information can be disclosed to the extent considered necessary by GEICAM.

To allow the use of the information derived from this study and to ensure the compliance with the current rules, the investigator is obliged to provide GEICAM with all the results of examinations and all the data developed in this study. Except in that required by law, the information obtained during the study can only be provided to the doctors and to the competent authorities by GEICAM.

GEICAM commits to publish the results of the study and to present them in scientific meetings either if they are positive or negative. The different disclosures and author lists will be discussed and prepared by the SC.

10.5.1 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, GEICAM will, at a minimum register interventional clinical trials sponsored by GEICAM anywhere in the world on ClinicalTrials.gov or other publicly accessible websites (European Union Clinical Trials Register and national clinical trials public website (if applicable)), as required by GEICAM policy and local health authorities.

10.5.2 Clinical Trial Results Disclosure

GEICAM will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by GEICAM Policy/Standard and applicable local laws and/or regulations.

10.6. Ethics Committees and/or IRBs

GEICAM or its designee or the Investigator will supply relevant documents for submission to the respective EC/IRB for the protocol's review and approval. This protocol, the Investigator's Brochure/Summary of Product Characteristics [SmPC], a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, will be submitted to a central or local EC/IRB for approval. The EC/IRB's written approval of the protocol and subject informed consent must be obtained and submitted to GEICAM or designee before commencement of the study (ie, before shipment of the sponsor-supplied study treatment or study specific screening activity). GEICAM or its designee will notify the site once GEICAM or its designee has confirmed the adequacy of site regulatory documentation and, when applicable, GEICAM or its designee has received permission from competent authority to begin the trial. Until the site receives notification, no protocol activities, including screening, may occur.

As per applicable regulatory requirements, GEICAM or its designee or the Investigator will submit the required reports of the progress of the study to the EC/IRB and will communicate the possible SAE, the life-threatening adverse events and deaths. At the end of the study, GEICAM or its designee or the Investigator must inform the EC/IRB of trial closure. Al these notifications will be performed according to the applicable regulatory requirements.

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Protocol Attachment 1. Study Schedule

Study Schedule of Events and Timelines. GEICAM/2013-02			During Study Treatment. All visits ± 3 days of scheduled treatment day.				Post-treatment visit (30 +/- 5 days) from the last study treatment dose[t]	After study treatment termination	
Cycle	**Baseline**		**Cycle 1**	**Cycle 2**	**Cycle 3**	**Subsequent Cycles**		**PFS Follow-up Period (12 weeks +/- 14 days from last tumor assessment)**	**OS Follow-up Period (6 months ± 14 days) from last tumor assessment**
Day of cycle			**1**	**1**	**1**	**1**			
ICD for Entry (before any study specific tests)[a]	**X**								
Procedure/Laboratory/ Diagnostic Test	**Within 28 days (±7 days)**								
Inclusion/Exclusion Criteria	**X**								
Medical and surgical history and demographics[b]	**X**								
Physical examination[c]	**X**		**X**	**X**	**X**	**X**	**X**		
ECOG PS	**X**		**X**	**X**	**X**	**X**	**X**		
Hematology[d]	**X**		**X Day 1[f] & 14 (only Exp Arm)**	**X Day 1 & 14 (only Exp Arm)**	**X**	**X**	**X**		
Blood Chemistry[e]	**X**		**X[f]**	**X**	**X**	**X**	**X**		
Standard 12-lead ECG	**X**		**If clinically indicated**						
QLQ-C30, QLQ-BR23 and EQ-5D questionnaires[g]	**X**				**X**	**X**	**X**	**X**	
Concomitant medications	**X**		**X**						
AEs and SAEs[h]	**X**		**X**						

RANDOMIZATION

Study Schedule of Events and Timelines. GEICAM/2013-02			**During Study Treatment. All visits ± 3 days of scheduled treatment day.**				**Post-treatment visit (30 +/- 5 days) from the last study treatment dose[t]**	**After study treatment termination**	
Cycle	**Baseline**		**Cycle 1**	**Cycle 2**	**Cycle 3**	**Subsequent Cycles**		**PFS Follow-up Period (12 weeks +/- 14 days from last tumor assessment)**	**OS Follow-up Period (6 months ± 14 days) from last tumor assessment**
Exemestane dosing			**X[i]**						
Palbociclib dosing			**X[j]**	**X**	**X**	**X**			
Capecitabine dosing			**X[k]**	**X**	**X**	**X**			
Fulvestrant dosing			**X[l]**	**X**	**X**	**X**			
Tumor Assessment[m]	**X**		**Every 8 weeks (±7 days) from the start of treatment and every 12 weeks (±7 days) after 120 weeks of treatment. Patients with bone lesions identified at baseline will repeat the bone scans as clinically indicated or to confirm a complete response.**					**X[n]**	
Date of death									**X[o]**
Translational Research									
Blood samples for Exemestane PK studies[p]			**X (Predose) Day minus-1, Day 1 & 14**	**X (Predose) Day 14**					
Blood samples for Palbociclib PK studies[p]			**X (Predose) Day 14**	**X (Predose) Day 14**					

Study Schedule of Events and Timelines. GEICAM/2013-02			During Study Treatment. All visits ± 3 days of scheduled treatment day.				Post-treatment visit (30 +/- 5 days) from the last study treatment dose[t]	After study treatment termination	
Cycle	**Baseline**		**Cycle 1**	**Cycle 2**	**Cycle 3**	**Subsequent Cycles**		**PFS Follow-up Period (12 weeks +/- 14 days from last tumor assessment)**	**OS Follow-up Period (6 months ± 14 days) from last tumor assessment**
Blood (Plasma) samples for Biomarker studies[q]			**X Day 1 (Predose) and Day 15 (±3 days)**	**X Day 15 (±3 days)**			**X**		
Whole blood for Pharmacogenomics analysis[r]			**X (Day1)**						
Tumor tissue for Biomarker analysis[s]	**X**								

Study Schedule of Events and Timelines. Protocol GEICAM/2013-02

a	Signed, written informed consent (approved by ERB) obtained prior to any study specific procedure.
b	Includes local laboratory ER/PgR/HER2 expression levels and methods used to assess them, previous treatments. Sex, Race and Age
c	Physical examination includes measurements of height (BL only), weight, area surface body (BL only), blood pressure, pulse rate and body temperature. **In arm B (capecitabine)**, the area surface body will be recalculated in the event that patients experience body weight variations greater than 10% during the treatment period.
d	Hemoglobin, WBC, absolute neutrophils, platelet count. **In the experimental arm, the hematology will be performed every two weeks** (±3days) **for the first two cycles** and from cycle 3 onward, every four weeks (±3days).
e	At baseline visit: Fasting glucose, alkaline phosphatase, ALT, AST, total bilirubin, serum creatinine, sodium, potassium, magnesium, total calcium,. At treatment visit or safety visit: Fasting glucose, alkaline phosphatase, ALT, AST, total bilirubin, serum creatinine, total calcium
f	Not on cycle 1 if the assessments were performed within the 7 days prior to day 1 of treatment. The initiation of the treatment will be within 7 days after randomization
g	Patients will complete each instrument within 28 days (± 7 days) prior to the first treatment administration, pre-dose on Day 1 of every two cycles starting with Cycle 3 until Day 1 of Cycle 7 (at cycles 3, 5 and 7), thereafter on Day 1 of every three cycles till the end of treatment (at cycles 10, 13, etc) and at the

	post-treatment visit (30 days from the last study treatment dose or before initiation of new anticancer therapy). Patients who discontinue study treatment for reasons other than radiographically and/or clinically documented PD or initiate a new anticancer therapy, will additionally complete these instruments after RECIST-defined disease progression.
h	After informed consent form signature, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected. Adverse events to be monitored continuously during the treatment period. All AEs occurring during the study and until the treatment discontinuation visit 30 days after the last study treatment to be recorded with grading according to NCI-CTCAE, thereafter all study treatment-related SAEs should continue to be collected.
i	Exemestane will be taken orally, daily, and continuously. In patients within the PK sub-study, exemestane will be administered daily during a 7-day lead-in period (day minus-7 through day minus-1) immediately preceding cycle 1.
j	Palbociclib will be taken orally, daily, and during 3 weeks (Day 1 to Day 21) followed by a 1 week rest period in 28-day cycles
k	Capecitabine will be taken orally, daily, and during 2 weeks (Day 1 to Day 14) followed by a 1 week rest period in 21 days cycles
l	Fulvestrant will be administered as two 5ml intramuscular injections, one in each buttock, on days 1 and 15 (±3 days) of Cycle 1, and then on Day 1 of each subsequent 28 day cycle (±3 days). Time windows extended to ±7 days after 24 weeks.
m	Disease assessment for all patients at baseline will include: • CT (or PET-CT) scan or MRI of the chest, abdomen and pelvis (CAP). • Bone scan (or PET scan) is mandatory if the patient has bone disease or if there is any suspicious of bone metastases. Any suspicious abnormalities (ie, hotspots) identified on the bone scans or PET scan at baseline must be confirmed by X-ray (if there are other measurable lesions), CT (or PET-CT) scan with bone windows or MRI (if only bone disease is present). • Brain CT scan or MRI is mandatory if the patient has CNS metastases or if there is any suspicious of CNS metastases. • CT scan or MRI of any other sites of disease as clinically indicated. • Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions. All lesions, including bone lesions followed by X-ray (if there are other measurable lesions), CT (or PET-CT) scan with bone windows or MRI (if only bone disease is present), will be followed every 8 weeks (± 7 days) from the start of treatment and every 12 weeks (±7 days) after 120 weeks of treatment**.**. Bone scans (if applicable) will be repeated 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) and to confirm a complete response.
n	Only to be performed post-study treatment if disease progression has not yet been confirmed and patients have not initiated a new therapy. Tumor assessments will be performed every 12 weeks (± 7 days) from the last tumor assessment and bone scans (if applicable) as clinically indicated bone scan.
o	The patients will be followed for survival every 6 months (±14days) from last tumor assessment until death, loss to follow-up, withdrawal of consent or study termination by GEICAM. After progression, the tumor assessment will be performed according to the standard medical practice. The date of death and all treatments received by the patient after progression (according to the standard medical practice) will be collected in the eCRF.
p	Only to be performed in selected sites and in Arm A (Cohort 1) in patients accepting to participate. Exemestane PK samples should be collected pre-dose on day minus-1, cycle 1 day 1 (back-to-back days), and on day 14 in cycles 1 and 2. Palbociclib PK samples should be collected pre-dose on day 14 in cycles 1 and 2. Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation. Refer to the Sample Management Manual for detailed collection, processing and shipping procedures.
q	In arms A and B. Blood (Plasma) samples for *ESR1* mutation analysis and exploratory biomarker analyses: Fourblood samples (tubes optimized for plasma collection) will be

	collected from all patients at: 1) baseline (Cycle 1, Day 1pre-dose or within the 7 days prior to the first dose of treatment), 2) Cycle 1 Day 15 (±3 days), 3) Cycle 2 Day 15 (±3 days) and 4) at the end of treatment (approximate 30 days after last study dose but always before the next anti-cancer therapy). If a patient ends the study treatment due to a reason different than disease progression, every effort should be made to collect an additional sample upon progression (regardless of the administration of other treatment) The baseline sample must be drawn prior to the first dose of any study treatment and the sample of Cycle 1 Day 15 (± 3 days) prior to the fulvestrant dose in patients included in arm A of Cohort 2. For patients included in the PK sub-study, the baseline plasma sample will be collected on day -7 predose or within 7 days prior to the first exemestane dose, because in these patients exemestane will be administered daily during a 7 day lead-in period (day minus 7 through day minus 1) immediately pre-ceding cycle 1.
r	In arms A and B. Whole blood for Pharmacogenomics analysis: A whole blood sample (K2 EDTA whole blood collection tubes optimized for DNA analysis) will be collected when feasible but preferable within 7 days prior to the first treatment dose to be retained for potential pharmacogenomic/biomarker analyses related to drug response or adverse drug reactions.
s	In arms A and B. Tumor Tissue for Biomarker Assessments: Formalin-fixed paraffin embedded (FFPE) tumor tissue, preferably from metastatic tumor, will be collected for retrospective biomarker assessments, Samples will be sent to the sponsor-designated central laboratories.
t	For safety reasons all patients will have a visit 30 (±5) days after finishing treatment with the study treatment. This post-treatment visit must be performed before initiation of any new anticancer therapy and may be advanced when a new anticancer therapy is scheduled before 30 (±5) days after finishing the study treatment.

Protocol Attachment 2. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5(6):649-65.

Protocol Attachment 3. List of Drugs Known to Predispose to Torsade de Pointes

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox	Anticancer	Cancer (leukemia)
Astemizole	Hismanal	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Bepridil	Vascor	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen	Antimalarial	Malaria
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection
Cisapride	Propulsid	GI stimulant	Increase GI motility
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn	Antiarrhythmic	Abnormal heart rhythm
Domperidone	Motilium, Motillium, Motinorm Costi, Nomit	Antinausea	Nausea, vomiting
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Zineryt, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Gatifloxacin	Tequin	Antibiotic	Bacterial infection
Grepafloxacin	Raxar	Antibiotic	Bacterial infection
Halofantrine	Halfan	Antimalarial	Malaria
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Ibogaine	None	Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Levomepromazine	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Levomethadyl acetate	Orlaam	Opioid agonist	Narcotic dependence
Levosulpiride	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic	Schizophrenia
Mesoridazine	Serentil	Antipsychotic	Schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin	Antineoplastic Agent	Cancer
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
			pneumonia)
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Probucol	Lorelco	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Abnormal heart rhythm
Roxithromycin	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin	Zagam	Antibiotic	Bacterial infection
Sulpiride	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Sultopride	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terfenadine	Seldane	Antihistamine	Allergic rhinitis
Terlipressin	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Vasoconstrictor	Septic shock
Terodiline	Micturin, Mictrol (not bethanechol)	Muscle relaxant	Bladder spasm
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa	Anticancer	Cancer (thyroid)

Note: Medicines on this list are reviewed on an ongoing basis by the Scientific Review Board of the Arizona Center for Education and Research on Therapeutics (AzCERT) to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checking the website at crediblemeds.org for the most up-to-date information. There may be many additional brand names that are not listed on this form.

http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm

Protocol Attachment 4. Capecitabine Dose Calculation According to Body Surface Area

Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1,250mg/m^2

100% Dose Level = 2,500 mg/m^2/day (twice daily 1,250 mg/m^2)			**Number of tablets to be taken at each dose (morning and evening)**	
Surface Area (m^2)	**Total Daily Dose (mg)***	**Twice Daily dose (mg)**	**150mg**	**500mg**
< = 1.25	**3000**	**1500**	**–**	**3**
1.26–1.37	**3300**	**1650**	**1**	**3**
1.38–1.51	**3600**	**1800**	**2**	**3**
1.52–1.65	**4000**	**2000**	**–**	**4**
1.66–1.77	**4300**	**2150**	**1**	**4**
1.78–1.91	**4600**	**2300**	**2**	**4**
1.92–2.05	**5000**	**2500**	**–**	**5**
2.06–2.17	**5300**	**2650**	**1**	**5**
> = 2.18	**5600**	**2800**	**2**	**5**
* Total Daily Dose calculated on mg/m^2 for the median value, and rounded to the nearest 100mg.				

75% Dose Level = 1,900 mg/m^2/day (twice daily 950 mg/m^2)			Number of tablets to be taken at each dose (morning and evening)	
Surface Area (m^2)	**Total Daily Dose (mg)***	**Twice daily dose (mg)**	**150mg**	**500mg**
< = 1.14	**2000**	**1000**	**_**	**2**
1.15 – 1.30	**2300**	**1150**	**1**	**2**
1.31 – 1.49	**2600**	**1300**	**2**	**2**
1.50 – 1.67	**3000**	**1500**	**–**	**3**
1.68 – 1.83	**3300**	**1650**	**1**	**3**
1.84 – 2.02	**3600**	**1800**	**2**	**3**
2.03 – 2.21	**4000**	**2000**	**–**	**4**
> = 2.22	**4300**	**2150**	**1**	**4**
* Total Daily Dose calculated on mg/m^2 for the median value, and rounded to the nearest 100mg.				

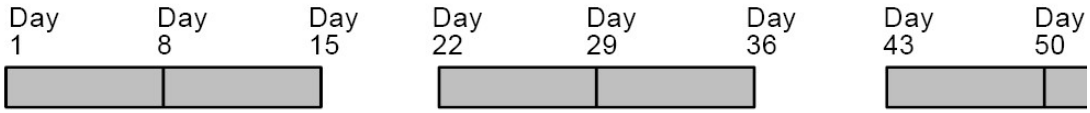
50% Dose Level = 1,250 mg/m^2/day (twice daily 625 mg/m^2)			Number of tablets to be taken at each dose (morning and evening)	
Surface Area (m^2)	**Total Daily Dose (mg)***	**Twice daily dose (mg)**	**150mg**	**500mg**
1.16 – 1.43	**1600**	**800**	**2**	**1**
1.44 – 1.71	**2000**	**1000**	**–**	**2**
1.72 – 1.95	**2300**	**1150**	**1**	**2**
1.96 – 2.23	**2600**	**1300**	**2**	**2**
> = 2.24	**3000**	**1500**		**3**
* Total Daily Dose calculated on mg/m^2 for the median value, and rounded to the nearest 100mg.				

Standard and reduced dose calculations according to body surface area for a starting dose of capecitabine of 1,000mg/m^2

	2,000mg/m^2/day (twice daily 1,000mg/m^2)				
	Full dose 2,000mg/m^2	**Number of 150mg tablets and/or 500mg tablets per administration (each administration to be given morning and evening)**		**Reduced dose (75%) 1,500mg/m^2**	**Reduced dose (50%) 1,000mg/m^2**
Surface Area (m^2)	**Total Daily Dose (mg)***	**150mg**	**500mg**	**Total Daily Dose (mg)***	**Total Daily Dose (mg)***
< = 1.26	**2,300**	**1**	**2**	**1,600**	**1,200**
1.27–1.38	**2,600**	**2**	**2**	**2,000**	**1,200**
1.39–1.52	**2,900**	**3**	**2**	**2,200**	**1,500**
1.53–1.66	**3,200**	**4**	**2**	**2,400**	**1,600**
1.67–1.78	**3,500**	**5**	**2**	**2,600**	**1,600**
1.79–1.92	**3,600**	**2**	**3**	**2,800**	**1,800**
1.93–2.06	**4,000**	**-**	**4**	**3,000**	**2,000**
2.07–2.18	**4,300**	**1**	**4**	**3,200**	**2,100**
> = 2.19	**4,600**	**2**	**4**	**3,500**	**2,200**

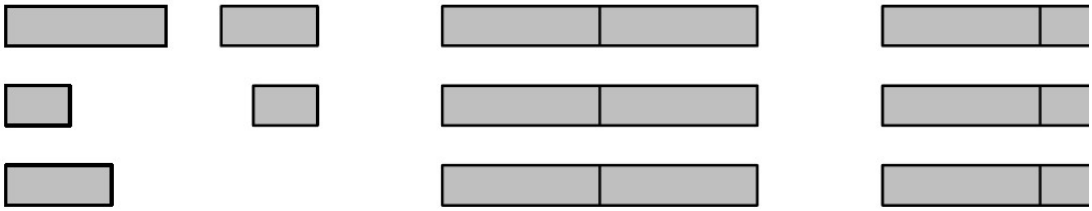
Protocol Attachment 5. Capecitabine Interruptions and Extended Rest Periods

Normal Treatment:



Interruptions During Treatment:

Interruptions are regarded as lost treatment days and the planned treatment schedule maintained.



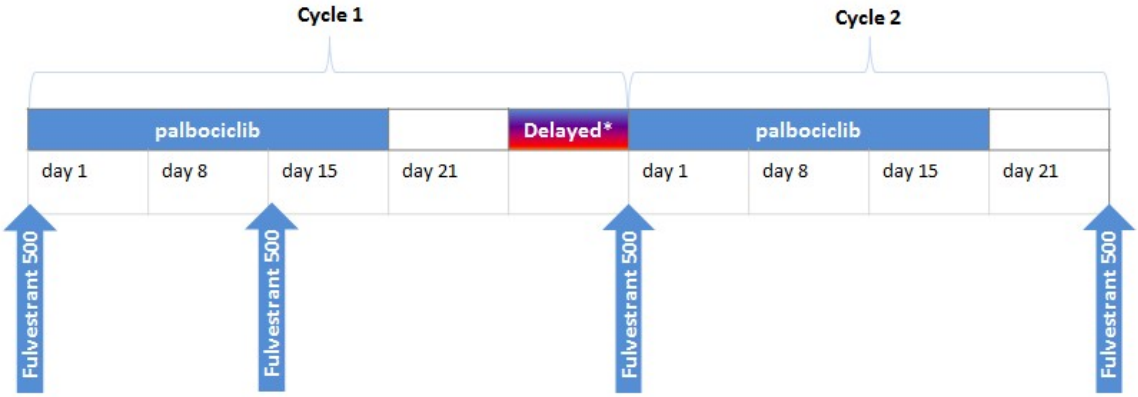
Extended Rest Periods:

If a rest period is extended due to toxicity, the “complete" cycle should be given afterw

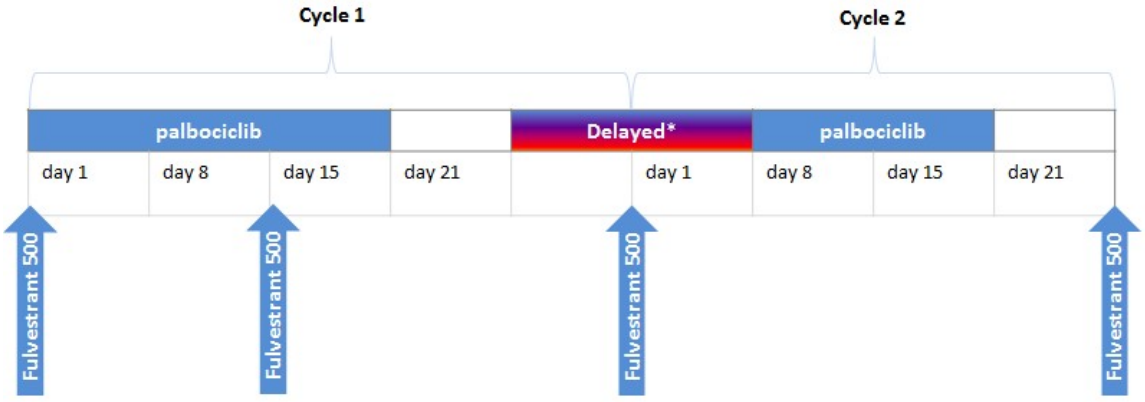
Protocol Attachment 6. Palbociclib/Fulvestrant Interruptions and Extended Rest Periods

Cohort 2: PALBOCICLIB Dosing Interruption

In the event of a toxicity requiring dosing delay of palbociclib, the administration of Fulvestrant should be continued as pre-planned schedule, though every effort should be made to re-synchronize the day 1 palbociclib administration and Fulvestrant injection using the allowed visit windows as defined in the study schedule



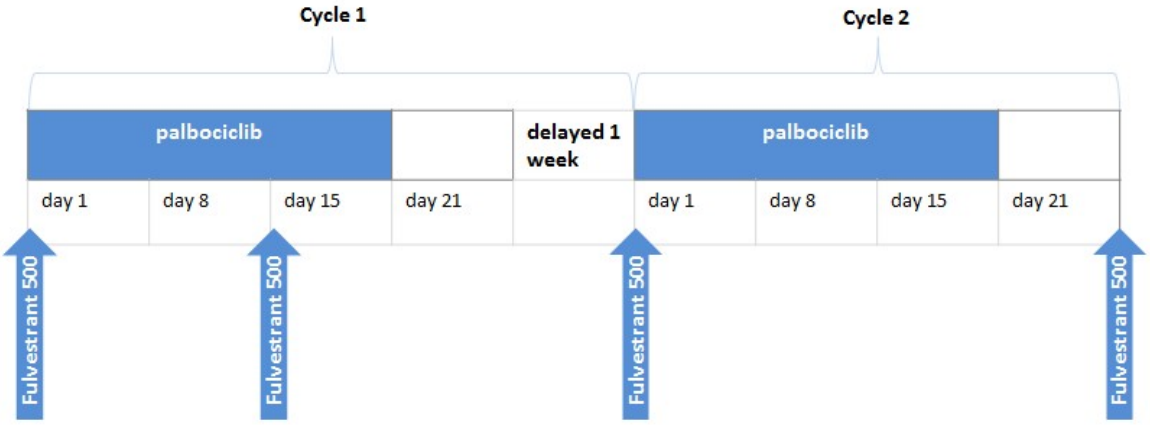
*Palbociclib delayed ≤ 3 days before 24 weeks
*Palbociclib delayed ≤ 7 days after 24 weeks



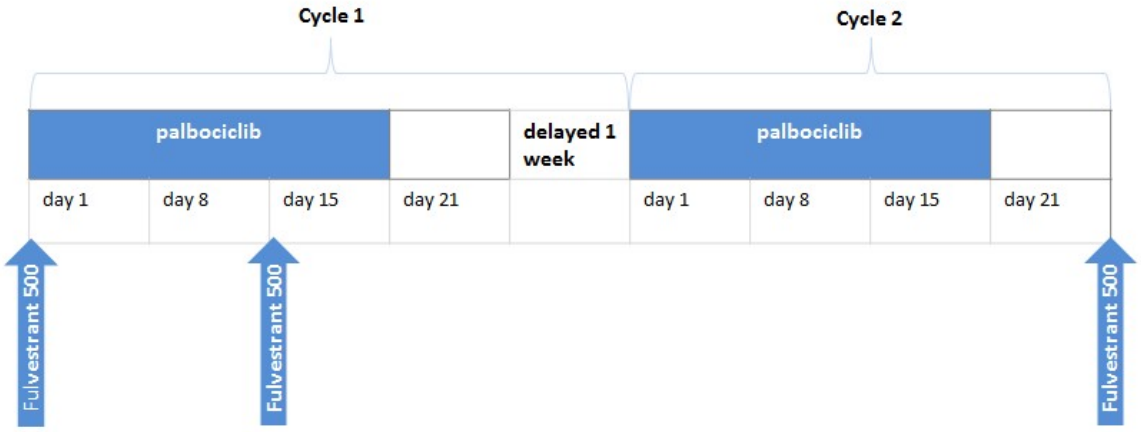
*Palbociclib delayed > 3 days before 24 weeks
*Palbociclib delayed > 7 days after 24 weeks

Cohort 2: FULVESTRANT Dosing Interruption

Fulvestrant can also be delayed by a maximum of 7 days, or longer if required for satisfactory recovery of the platelet count, as it should not be administered if the platelet count is< 50,000/mm^3.



A single Fulvestrant dose can be skipped a single time in case of a Fulvestrant related toxicity.



Protocol Attachment 7. Palbociclib, Exemestane and Capecitabine Diaries

In separate document.

Protocol Attachment 8. Adverse event (AE) non defined in CTCAE

CTC Grade	Equivalent to:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity.
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient.
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life-threatening / disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing daily activities; treatment or medical intervention is required in order to maintain survival.
Stage 5	Death	AE resulting in death.

Protocol Attachment 9. Adverse Events / Serious Adverse Events Assessment Guide

Time	After ICD Before Drug	During Therapy	30-Day Post-discontinuation Follow-up Period	Long-Term Follow-up Period
Events to Collect	AE/SAEs	New/Ongoing AE/SAEs		New/Ongoing SAEs
	Related to Procedures	Regardless of Relatedness to Study Treatment or Procedures		Related to Study Treatment or Procedures

Abbreviations: AE = adverse event, ICD = informed consent document, SAE = serious adverse event.

Protocol Attachment 10. QLQ-C30, QLQ-BR23 and EQ-5D Questionnaires

In separate document.