CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207,103
Priority or Standard	Priority
Submission Date	Part 1, June 30th, 2014
(Rolling Submission)	Part 2, August 13th, 2014
PDUFA Goal Date	April 13th, 2015
Division / Office	DOP1/OHOP
Reviewer Name(s)	Julia Beaver, MD (efficacy) Laleh Amiri-Kordestani, MD (safety) Patricia Cortazar, MD (CDTL)
Review Completion Date	January 15th, 2015
Established Name	Palbociclib
(Proposed) Trade Name	Ibrance
Therapeutic Class	Kinase Inhibitor
Applicant	Pfizer, Inc.
Formulation(s)	100mg and (b) (4) capsule
Dosing Regimen	125mg orally daily for 21 days followed by 7 days off treatment
Indication(s)	In combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on review of the clinical data, the clinical review team recommends approval of palbociclib (Ibrance) under accelerated approval regulation 21CFR 314 (Subpart H) for the following indication:

> *IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.*

The basis for this recommendation is a favorable benefit-risk profile for palbociclib when added to letrozole in first-line ER-positive, HER2-negative advanced breast cancer (see Section 1.2, 'Risk Benefit Assessment'). In the pivotal randomized Phase 2 study, PALOMA-1 (A5481003), a clinically meaningful and statistically significant 10 month improvement in median Progression Free Survival (PFS) was observed with a Hazard Ratio (HR) of 0.488 (95% Confidence Interval (CI): 0.319, 0.748, 1-sided p=0.0004) favoring the palbociclib plus letrozole treatment arm. The effect on progression free survival was consistent across relevant subgroups. The safety profile of palbociclib when added to letrozole was acceptable and the toxicities were transient and reversible. Palbociclib did increase adverse events particularly the incidence of neutropenia (an increase in neutropenic fevers was not seen in the pivotal study), however the drug was generally well tolerated and the adverse events were manageable. Continued approval for this indication will be contingent upon demonstration of improvement in PFS in the confirmatory trial (PALOMA-2), which is currently fully accrued and final results are expected in the first or second quarter of 2016. The results submitted to this NDA demonstrate a clinically meaningful benefit with an acceptable safety profile and accelerated approval would provide palbociclib to patients approximately two years earlier than awaiting the final Phase 3 trial results.

1.2 Risk Benefit Assessment

Advanced breast cancer is incurable and therefore is considered a serious and life-threatening condition. In 2014, it is estimated that 40,000 women will die of breast cancer[1]. Despite the availability of hormone directed therapies for treatment of first-line HR-positive advanced breast cancer, patients ultimately develop resistance and progression of disease and go on to receive multiple additional therapies including many lines of toxic chemotherapies. It has been over 15 years since a drug was approved for this specific indication. There is a clear medical need to address to develop new therapies for the treatment of advanced breast cancer in order to extend life, delay disease progression and/or lessen breast cancer related symptoms. Under

Subpart H of the Code of Federal Regulations it is possible to grant accelerated approval of a drug for a life-threatening illness based on an effect on a surrogate endpoint that is reasonably likely to predict meaningful clinical benefit to patients over existing treatments.

The assessment of benefit in this NDA is based on the randomized portion of the PALOMA-1 study (A5481003). PALOMA-1 is an international, multicenter, open-label, randomized Phase 1/2 study in a population of postmenopausal HR-positive HER2-negative advanced breast cancer patients. In the randomized Phase 2 portion of this pivotal study, a total of 165 patients who had not been treated previously for their advanced disease were enrolled. Patients were randomized 1:1 to receive palbociclib plus letrozole or letrozole alone. The study was broken up into two parts; Part 1 included an unselected patient population (N=66) and Part 2 included a biomarker selected population (N=99). The primary endpoint was investigator-assessed PFS of the combined Part 1 and Part 2 cohorts. The HR for this primary endpoint was 0.488 (95% CI 0.319, 0.748; 1-sided p-value 0.0004), with a median PFS of 20.2 months (95% CI 12.8, 27.5) for the palbociclib plus letrozole arm and 10.2 months (95% CI 5.7, 12.6) for the letrozole alone arm. The improvement in PFS is clinically meaningful and represents a large improvement over current therapy. However, there are limitations to the pivotal study. Many of the uncertainties in the clinical trial are due to the fact that the study was not planned or conducted with the expectation of supporting regulatory approval. As a result there were data-driven changes to the statistical analysis plan, protocol deviations and issues with respect to compliance and conduct of the study. In addition, while Blinded Independent Central Review (BICR) analysis supported the primary endpoint of PFS (in the combined Part 1 and Part 2 population), the BICR analysis of Part 1 of the study alone did not support the corresponding investigator-assessed PFS results. This discrepancy likely resulted from disagreements of progression events and censoring which could indicate a level of investigator bias. Despite these concerns and uncertainties, multiple sensitivity analyses supported the finding of clinical benefit.

Overall, the safety profile of palbociclib appeared to be acceptable relative to the benefit. Palbociclib did increase the incidence of cytopenias (particularly neutropenia), infections, diarrhea, nausea, eye disorders, and pulmonary embolisms. There is assurance given the data that the neutropenia can be appropriately managed as evidenced by a lower frequency of discontinuations in Part 2 of the study which took place after many of the dose modification issues were worked out in Part 1. There are no postmarketing safety requirements, however more information will be gained from multiple large planned or ongoing Phase 3 trials examining palbociclib in both the adjuvant and advanced breast cancer settings.

In conclusion, palbociclib in combination with letrozole for the first-line treatment of advanced breast cancer in postmenopausal patients with (b) (4)-positive HER2-negative disease demonstrates a favorable risk-benefit profile with enough evidence to recommend accelerated approval. Despite the concerns with the pivotal study, even if the demonstrated PFS benefit were halved there would still be a clinical benefit to this therapy given the life-threatening nature of advanced breast cancer and the acceptable

safety profile. Therefore, granting accelerated approval to palbociclib is justified due to the positive benefit risk and withholding this treatment from patients while awaiting results from the confirmatory trial will not be appropriate. However, continued approval for this indication may be contingent upon verification and description of clinical benefit in the Phase 3 trial PALOMA-2 (A5481008).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are being recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team recommends the following Postmarketing Requirement (PMR):

1. Submit the progression free survival (PFS) and overall survival (OS) data and results from the ongoing Trial A5481008, PALOMA-2, "A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease" when supplemental application for regular approval is submitted. In addition, submit OS data and results at study completion.

   Rationale: The final PFS results of Trial A5481008, PALOMA-2 will if statistically significant and clinically meaningful, confirm the clinical benefits of palbociclib treatment in combination with letrozole and will fulfill the requirement for the recommended accelerated approval.

The clinical team recommends the following Postmarketing Commitment (PMC):

1. Conduct analysis from the ongoing Trial A5481008, PALOMA-2, "A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease" to determine the prognostic or predictive significance of genetic alterations in the Cyclin D1/CDK4/6/p16/retinoblastoma pathway in ER (+), HER2 (-) breast cancer, specifically the prognostic/predictive significance of the genetic alteration to the safety and efficacy of palbociclib.

   Rationale: Further biomarker exploration is needed given that the pivotal study PALOMA-1 did not identify a biomarker for prediction or prognosis, but did indicate the potential that patients with *CDKN2A* loss might benefit less from palbociclib. These findings are preliminary in a small sample size and would require confirmation in a future study.

2 Introduction and Regulatory Background

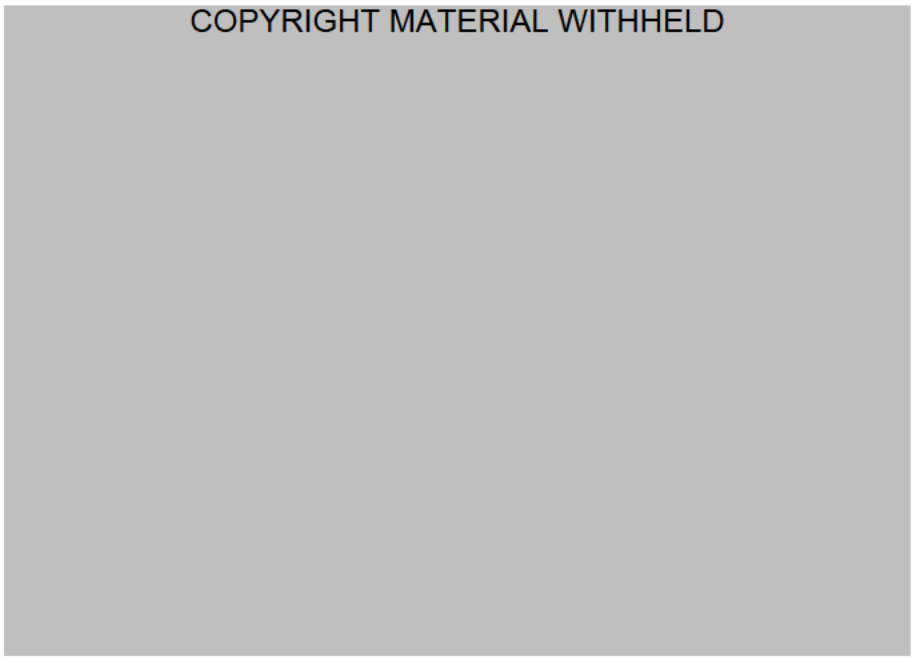
2.1 Product Information

The cyclinD1-cyclin-dependent kinases 4 and 6 (CDK4/6)-retinoblastoma (Rb) pathway is critical to the regulation of the cell cycle and deregulation of this pathway has been implicated in cancer. CDK4 and CDK6 are activated early in the cell cycle by Cyclin D1 and other cyclins thus facilitating the cell cycle progression from gap 1 (G1)- to synthesis (S)- phase. Activated cyclin-CDK complexes lead to phosphorylation and inactivation of Rb and result in the transcription of factors involved in S-phase entry. Cyclin D1 is the product of the *CCND1* gene and can regulate the growth of estrogen responsive tissues through binding to the hormone-binding domain of ER. Additional regulators of the cell cycle include the CDK inhibitors (CdkIs) such as the INK4 family. The INK4 proteins include $p16^{INK4A}$ (the product of the *CDKN2A* gene) and block the formation of the cyclinD-CDK4/6 complexes[2]. The cyclinD1-CDK 4/6-Rb pathway is depicted in Figure 1[3].

Frequencies of *CCND1* amplification and *CDKN2A* loss vary based on the breast cancer subpopulation studied and the methods and cut-offs used. Amplification of *CCND1* has been found in 15 to 20% of human mammary carcinomas and overexpression in up to 50%[4-6]. Within breast cancer, *CCND1* amplification varies between subtypes with ~58% amplification in luminal B tumors compared to 29% in luminal A tumors[7]. *CDKN2A* loss is found in approximately 4% of breast cancer tumors[8].

While the prognostic ability of cyclin D1 overexpression in unstratified breast cancer samples is not clear this is likely due to the fact that cyclin D1 overexpression is strongly associated with the ER-positive, better prognosis subtype [5,9,10]. Within the ER-positive subtype one study identified ER-positive breast cancer patients with cyclin D1 overexpression to have a shorter time to metastasis and decreased survival and another demonstrated that CCND1 amplification was a significant independent predictor of survival [11,12]. Additional studies have shown an association between high cyclin D1 expression and poor outcome in women treated with tamoxifen[13-15]. However some studies have either not detected an association with tamoxifen response or shown a worse prognosis for CCND1 amplified patients[16-19].

Figure 1: Cyclin D- Cyclin Dependent Kinases 4/6- Retinoblastoma Pathway



CDK: Cyclin dependent kinase; Cip/Kip: Kinase inhibitor protein family; E2F: Elongation factor 2; INK4: Inhibitors of CDK4; P: Phosphate; Rb: Retinoblastoma protein; STAT: Signal transducer and activator of transcription.
Source: Rocca et al. [3]

Palbociclib is an oral CDK 4/6 inhibitor whose mechanism of action appears to prevent the cell cycle progression from G1 to S phase. Preclinical experience indicated that palbociclib had anti-tumor activity in xenografts and luminal ER-positive cell lines were the most sensitive to CDK4/6 inhibition[20,21]. The most sensitive of the ER-positive cell lines were demonstrated to have high levels of Rb and low levels of *CDKN2A* [21]. In cell lines with Rb loss, a CDK4/6 independent state was induced and ultimately this led to palbociclib resistance [22].

2.2 Tables of Currently Available Treatments for Proposed Indications

The treatment of patients with advanced breast cancer (locally advanced not amenable to curative treatment and metastatic disease) is palliative in nature. In postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer, hormonal therapies are used prior to chemotherapies provided there is no visceral crisis[23]. These hormonal therapies include the selective estrogen receptor modulator tamoxifen and the aromatase inhibitors, anastrozole, letrozole and exemestane (as shown in Table 1). There are no approved products in combination with letrozole for the first-line treatment of advanced (b) (4)-positive, HER2-negative breast cancer.

Table 1: Available Therapy for the Proposed Patient Population

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Basis for approval	Important Safety and Tolerability Issues	Drug Class
FDA Approved Treatments						
Letrozole	First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer	1997	2.5mg daily by mouth	Vs. tamoxifen **TTP**: 9.4 months vs. 6.0 months HR 0.72 (p<0.0001) **OS**: 35 months vs. 32 months (P=0.5136)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Anastrozole	First-line treatment of postmenopausal women with HR-positive or unknown locally advanced or metastatic breast cancer	1995	1mg daily by mouth	Vs. tamoxifen **TTP**: 11.1 vs. 5.6 months (p=0.006) and 8.2 vs. 8.3 months (p=0.92)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Tamoxifen	In the treatment of metastatic breast cancer in women and men. Patients whose tumors are estrogen receptor positive are more likely to benefit.	1977	20mg daily by mouth	Response rate in 14 Phase 2 studies and nine literature reports. The overall database included 1164 patients	Uterine malignancies, stroke, pulmonary embolism and hot flashes	Selective estrogen receptor modulator
Other Treatments						
Exemestane	Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy	1999	25mg daily by mouth	Vs. megestrol acetate **TTP**: 20.3 weeks vs. 16.6 weeks (HR 0.84)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor

TTP: Time to Tumor Progression; OS: Overall Survival
Source: drugs@fda.com

2.3 Availability of Proposed Active Ingredient in the United States

Palbociclib is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Palbociclib is a first in class CDK4/6 inhibitor and no other CDK4/6 inhibitors are currently marketed in the United States.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

March 9th, 2004: IND 69324 for PD-0332991 (palbociclib) was submitted in the United States for the treatment of (b) (4) .

April 9th, 2008: The protocol for Study A5481003 was submitted to the IND (SN39/SN0030). Amendments to this protocol are explained in detail in Section 5.3.1. There was no special protocol assessment requested for Study A5481003 (PALOMA-1) supporting the current NDA submission.

October 2nd, 2012: A Type B End of Phase 2 (for Study A5481003) took place to discuss the potential submission of the Phase 2 trial results to support a Subpart H approval. FDA requested a pre-specified statistical analysis plan (SAP) and any amendments to the SAP for the Phase 2 trial as well as detailed safety information. FDA also recommended there be a central review of the Phase 2 PFS data as soon as possible. At this time FDA conveyed that the Phase 2 trial would be considered as two individual studies and recommended incorporating an early efficacy analysis (if expecting a large effect) or sizing the Phase 3 trial for the larger effect. FDA recommended an additional meeting be requested in order to discuss the potential of NDA submission in more detail.

Discussion also revolved around the plan for development of the Phase 3 confirmatory trial for the treatment of hormone receptor positive metastatic breast cancer patients with palbociclib. FDA recommended for the Phase 3 study that Pfizer define an appropriate patient population, determine HER2 negativity based on ASCO/CAP guidelines and reduce the number of stratification factors in order to have a sufficient number of patients for each combination of stratification factors. FDA agreed with the general SAP for the Phase 3 trial and agreed that investigator PFS was an appropriate endpoint for the confirmatory trial if strategies for addressing bias such as a centralized review were employed.

Additional discussion at this End of Phase 2 Meeting revolved around the potential for Pfizer to submit the Phase 2 trial results for a Subpart H approval. FDA requested a pre-specified SAP and any amendments to the SAP for the Phase 2 trial as well as detailed safety information. FDA also recommended there be a central review of the Phase 2 PFS data as soon as possible. At this time FDA conveyed that the Phase 2 trial would

be considered as two individual studies and recommended incorporating an early efficacy analysis (if expecting a large effect) or sizing the Phase 3 trial for the larger effect. FDA recommended an additional meeting be requested in order to discuss the potential of NDA submission in more detail.

February 8th, 2013: Pfizer submitted a breakthrough therapy designation request.

April 1st, 2013: FDA granted the breakthrough therapy designation based on the fact that breast cancer meets the criteria for a serious or life-threatening disease and the preliminary clinical evidence submitted on PD-0332991 Phase 1/2 trial that appeared to demonstrate substantial improvement in progression-free survival when compared to existing therapies.

May 17th, 2013: A Type B Pre-NDA meeting was held. At this meeting FDA agreed to accept the NDA submission based on the top line results from Study A5481003 as the results appeared to be promising. The FDA expressed concern regarding the multiple looks at the data which FDA stated may make interpretation from a statistical point of view difficult. Pfizer proposed a gatekeeping strategy to maintain statistical rigor with a proposal to analyze the study as a whole and if positive move to individual cohort analyses. FDA recommended Pfizer conduct the analysis as two separate studies since duplication of results in the second study could strengthen the application and cautioned that the interpretation of p-values will be difficult since there were many looks at the data making the analysis not entirely pre-specified. Pfizer proposed setting the final analysis of the primary endpoint PFS when approximately 90 events had occurred (instead of the 114 previously stated). The FDA did not agree with the plan to decrease the number of PFS events as the proposal was based on the observed data and was not pre-planned. FDA and Pfizer agreed that BICR assessments should be done on 100% of the patients in the Phase 2 trial, however FDA stated they recommended that the BICR analysis should be the primary analysis and if investigator-assessed PFS was kept as the primary analysis convincing argument that minimal bias is present would need to be given. FDA agreed that the estimated subject experience with respect to safety data was acceptable to support an NDA submission. FDA encouraged Pfizer to open an expanded access program for palbociclib.

November 14th, 2013: A Type B Breakthrough Meeting follow-up discussed the overall development plan for palbociclib. Pfizer clarified that the interim analysis for the PALOMA-2 confirmatory A5481008 trial would not be available during the A5481003 Phase 2 based NDA review.

December 17th, 2013: A Type B Pre-NDA Meeting was held and discussed the format and content of the NDA submission. For safety data it was recommended that Pfizer pool the safety data from studies with similar patient population, disease status and baseline risk factors. Other specifics of the NDA submission regarding datasets were agreed upon. FDA also agreed with Pfizer's proposal to submit a stand-alone exposure-response analysis report for safety and efficacy.

February 28, 2014: A Type B Pre-NDA Meeting was held to discuss the Top Line Results from the PALOMA-1 A5481003 study. FDA requested an analysis of the imbalance in censoring on the two arms and reasons for censoring observations in both investigator assessments and BICR analysis. FDA expressed concern that drug administration condition for the initial approval Phase 2 PALOMA-1 A5481003 trial was under the fasting condition and the confirmatory trial PALOMA-2 A5481008 was under the fed condition with a new free base to-be-marketed formulation. Pfizer responded they would address these issues prior to NDA submission.

May 6th, 2014: A Type B Pre-NDA Meeting was held to discuss CMC issues. FDA agree that the bridging data between the capsule formulation used in fasting conditions in the Phase 2 PALOMA-1 trial with the free base capsule used in the Phase 3 PALOMA-2 trial to be adequate to support the proposal of commercializing the free base capsule (used in the Phase 3 PALOMA-2 study) although FDA stated the final determination would be an NDA review issue.

June 25th, 2014: A rolling submission was granted to Pfizer and it was clarified that the review clock would begin after the complete submission was received.

September 12th, 2014: FDA agreed with the applicants initial pediatric study plan and acknowledged the request for a full waiver from PREA requirements in ER-positive, HER2-negative advanced breast cancer.

October 9th, 2014: The NDA was given priority review with PDUFA deadline of April 13th, 2015.

Reviewer Comment: *There were no meetings to discuss the initial development of the Phase 2 pivotal trial as this trial was not originally planned for registration.*

2.6 Other Relevant Background Information

In 2014, Breast Cancer was diagnosed in 232,670 women in the United States (U.S.) and it is estimated that 40,000 women will die of their disease this year.[1] In the U.S. 60.8% of patients are diagnosed with early stage localized disease, 32% of patients have spread to regional lymph nodes and are still considered early stage, 2% have unknown stage and 5% are diagnosed with de-novo metastatic disease.[1] The median age of breast cancer at diagnosis is 61. Breast cancer can be categorized into different histopathologic subtypes based on expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 overexpression. ER and PR positive cancers comprise the majority of breast cancer cases at approximately 60-65%.[24] Patients with ER and PR positivity have specific treatment options centered on hormone directed therapy. Postmenopausal patients have multiple options for hormone directed therapy due to the main source of their estrogens resulting from the conversion of androgens to estrogens via aromatase enzyme activity. Postmenopausal patients with advanced breast cancer have the option for treatment with three steroidal and non-steroidal aromatase inhibitors (letrozole, anastrozole and exemestane) or tamoxifen a selective estrogen receptor

modulator. Exemestane is not approved for first-line treatment however is used in this setting occasionally. Patients with hormone receptor positive advanced disease should be treated in the first-line setting with hormonal therapy if appropriate.[23] Patients in whom visceral crisis is impending should not be treated with hormonal therapy and instead be treated with chemotherapy. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear to be acceptable. Requests for additional information from the applicant throughout the review process were addressed in a timely fashion.

3.2 Compliance with Good Clinical Practices

According to the Applicant, the study was conducted in full conformance with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in conformance with the principles of the Declaration of Helsinki as amended in 2008. Written informed consent was obtained from each participant in the study. The protocol and subsequent amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

The pivotal randomized Phase 2 study was conducted at 50 centers in 12 countries (Canada [2 sites], France [2 sites], Germany [8 sites], Hungary [7 sites], Ireland [4 sites], Italy [1 site], Russia [4 sites], South Africa [1 site], South Korea [2 sites], Spain [5 sites], Ukraine [4 sites], and the United States [10 sites]).

Please see Section 6.1.3 for a discussion of the protocol deviations.

The Office of Scientific Investigations (OSI) audit was requested for this NDA. See Clinical Inspection Summary written by Lauren Iacono-Connors, Ph.D, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI. The OSI inspected four of the highest accruing sites. Due to current restrictions on travel to Ukraine, two sites in Ukraine each enrolling 7 patients were not able to be inspected. The applicant and the CRO ((b) (4)) who performed the function of the Blinded Independent central Review (BICR)/Central Imaging Vendor were also inspected and found on interim classification to have no major issues. A summary of the site inspections is provided in Table 2.

Table 2: Summary of OSI findings

Inspection	Site #, and # of Subjects	Inspection Date	Interim Classification
Professor John Paul Crown St. Vincent's University Hospital Dublin, Ireland	Site#: 1033 Number of Subjects: 13	October 20-23, 2014	NAI. No Major Issues.
Dr. Istvan Lang Országos Onkológiai Intézet Budapest, Hungary	Site#: 1011 Number of Subjects: 9	November 3-7, 2014	NAI. No Major Issues.
Dr. Katalin Boer Szent Margit Kórház Budapest, Hungary	Site#: 1008 Number of Subjects: 8	October 26-30, 2014	NAI. No Major Issues.
Dr. Richard Samuel Finn Ronald Reagan UCLA Medical Center Los Angeles, CA, USA	Site#: 1001 Number of Subjects: 7 (Phase 2) and 13 (Phase 1)	September 2-November 18, 2014	OAI. Major Issues

NAI: No action indicated and no deviation from regulations. OAI: Official action indicated

Dr. Finn's site (1001) was issued a Form FDA 483 citing five inspectional observations for "failure to follow the investigational plan, failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation (AEs and concomitant medications), subjects not signing the most current informed consent document or being properly reconsented when informed consents were updated, inaccurate investigational drug disposition records and Form FDA 1572s not being updated in a timely fashion to reflect changes in study staff and clinical laboratory facilities". The preliminary classification (based on information in 483 or preliminary communication with the field with complete Establishment Inspection Report pending) for this inspection was official action indicated (OAI). The preliminary classifications for the remaining inspections are no action indicated (NAI). A summary of issues found at Dr. Finn's site 1001, the largest accruing U.S. site are listed below:

- Seven out of 20 patients revealed discrepancies between the source documents and the eCRF regarding doses taken.
- One patient received inappropriate dosing of study drug for approximately 2 weeks.
- One patient had incorrect determination of site of disease and failure to determine measurable disease with inappropriate imaging. This patient did not receive any study medication.
- Two additional patients were stratified incorrectly.
- Six patients missed laboratory assessments for various lab tests
- A serious adverse event was reported to the applicant outside of the 24 hour window.
- PK samples were collected out of the window for three subjects
- Fifteen out of 20 subject records reviewed revealed discrepancies between source documents and the eCRF pertaining to adverse events. These discrepancies were usually limited to Grade 1 and Grade 2 AEs. However in subject 1001-1002, the eCRF document or lab value showed Grade 3 leukopenia

and neutropenia and the AE log showed Grade 2. Also in this patient an event of neutropenia Grade 3 was not recorded into the eCRF.

- Three patients showed discrepancies between source documents and the eCRF pertaining to concomitant medications
- Two patients out of 20 did not sign the most recent IRB approved informed consent form and three patients were not re-consented with change in procedure pertaining to administration of drug with or without food.
- The site did not appropriately update changes in sub investigators and laboratory facilities

Reviewer Comment*: When each of the deviations noted at site 1001 are examined independently, no patient was placed at significant risk and key study outcome measures were not affected. However, due to the totality of inspectional observations demonstrating poor ability of site 1001 to adhere to the investigational plan, the OSI recommendation was to not use the data generated at site 1001 in the review of the study. A sensitivity analysis was performed removing all the patients from site 1001. This analysis does not change the conclusions of the study as presented in Section 6.1.11.*

3.3 Financial Disclosures

All investigators were assessed for equity interest, significant payments, proprietary interests, and other compensation. Of the 1143 investigators listed in the study, certification was provided for 1141 (99.8%). Due diligence was required for 79 of the 1141 investigators. Twenty three of the 1243 investigators listed in the study report had financial information to disclose (1.8%). There were 381 investigators (58 principal investigators and 323 sub-investigators) in the pivotal study PALOMA-1. One hundred percent of these investigators were screened for financial disclosures. Eight had financial information to disclose and are summarized in the following table (Table 3).

Table 3: Summary of Financial Disclosures from Study A5481003

Clinical Site Number	Investigator Name (PI or SI)	Phase 2 Patient Enrollment at Site	Disclosure
(b) (6)			Honorariums totaling $29,630.50
			Advisory board, scientific grants and individual services totaling $92,500
			Consulting, honorarium, symposia speaker totaling $89,617
			Equity in Pfizer totaling $286,048.54 (as disclosed on 1/7/2010). The shares are in a charitable foundation account.
			Miscellaneous payments totaling $35,712.28
			Miscellaneous payments totaling $212,124.37
			Consulting and grants totaling $41,147.09
			Consulting totaling $34,924.41

PI: Principle Investigator; SI: Sub-investigator. Source: NDA 207103 Section 1.3.4, Financial Disclosure

***Reviewer Comment**: Investigators with significant disclosable interests enrolled approximately 23% (N=39) of the total number of patients in the randomized trial. While this is not an insignificant amount of patients each individual investigator enrolled between 2-5% of the population which is small and unlikely to individually affect the results of the study. When a sensitivity analysis was performed removing each site with conflicted investigator as well as all of the clinical sites with conflicted investigators, the PFS effect remained in favor of the palbociclib plus letrozole arm providing reassurance of the effect (see details in Section 6.1.11)*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

For full details, please see the CMC reviews by Dr. Joyce Crich and Dr. Xiao Chen.

4.2 Clinical Microbiology

Please see Product Quality Microbiology Review by Dr. Jessica Cole. The microbiological quality of the drug product was assured via (b) (4) manufacturing controls. The manufacturing process is (b) (4) and 26 batches were demonstrated to meet the compendial limits for solid oral dosage forms. Therefore, from a product quality microbiology perspective the submission was recommended for approval.

4.3 Preclinical Pharmacology/Toxicology

For full details, please see Pharmacology/Toxicology review by Dr. Wei Chen. The nonclinical studies adequately support the safety of oral administration of palbociclib for the proposed indication and the recommendation from the team is for approval.

Non-clinical studies of palbociclib included safety pharmacology studies, genotoxicity studies, reproductive toxicity studies, pharmacokinetic studies, toxicokinetic studies and repeat-dose general toxicity studies which were conducted in rats and dogs. The pivotal toxicology studies were conducted in compliance with Good Laboratory Practice regulation.

Pharmacology:
As described above, palbociclib is an inhibitor of CDK4 and CDK6. Palbociclib modulates downstream targets of CDK4 and CDK6 in vitro and induces G1 phase cell cycle arrest and therefore acts to inhibit DNA synthesis and cell proliferation. Combination of palbociclib with anti-estrogen agents demonstrated synergistic inhibition of cell proliferation in ER+ breast cancer cells. Palbociclib showed anti-tumor efficacy in animal tumor model studies. Safety pharmacology studies with palbociclib demonstrated adverse effects on both the respiratory and cardiovascular function of dogs at a dose of 125mg/day (four times and 50-times the human clinical exposure respectively) based on mean unbound C_{max}.

General toxicology:
Palbociclib was studied in single dose toxicity studies and repeated dose studies in rats and dogs. Adverse effects in the bone marrow, lymphoid tissues, and male reproductive organs were observed at clinically relevant exposures. Partial to complete reversibility of toxicities to the hematolymphopoietic and male reproductive systems was demonstrated following a recovery period (4-12 weeks), with the exception of the male reproductive organ findings in dogs. Gastrointestinal, liver, kidney, endocrine/metabolic (altered glucose metabolism), respiratory, ocular, and adrenal effects were also seen. See Section 7.7 for a more detailed description of hyperglycemia effects.

Genetic toxicology:
Palbociclib was evaluated for potential genetic toxicity in *in vitro* and *in vivo* studies. The Ames bacterial mutagenicity assay in the presence or absence of metabolic activation demonstrated non-mutagenicity. In addition, palbociclib did not induce chromosomal aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. Palbociclib was identified as aneugenic based on kinetochore analysis of micronuclei formation in an *in vitro* assay in CHO-WBL cells. In addition, palbociclib was shown to induce micronucleus formation in male rats at doses ≥ 100 mg/kg/day (10x human exposure at the therapeutic dose) in an *in vivo* rat micronucleus assay.

Reproductive toxicology:

No adverse effects were seen on estrous cycling, mating, fertility and early embryonic development when palbociclib was administered to female rats before and during the mating time frame, and continuing until gestation day (GD) seven. Repeat dosing of palbociclib did cause toxicities in male rat and dog reproductive organs. These toxicities were generally dose-dependent and did not fully recover after 12-weeks of a non-dosing period. When administered to animals during the period of organogenesis, palbociclib resulted in reduced fetal body weights, and lead to increased fetal incidence of cervical ribs (skeletal variation) in rats, and a low incidence of small phalanges on the forepaws in rabbits. Based on palbociclib' s mechanism of action and the role of CDK4/CDK6 in development, it is likely that palbociclib can cause fetal harm.

Carcinogenicity studies:
No carcinogenicity studies were submitted as supportive data for this NDA as the indicated population has advanced cancer.

4.4 Clinical Pharmacology

For full details, please see Clinical Pharmacology/ Pharmacometrics Reviews by Drs Ping Zhao, Jerry Yu, Rosane Charlab Orbach, and Jeanne Fourie Zirkelbach.

4.4.1 Mechanism of Action

Palbociclib is a reversible inhibitor of CDK4 and CDK6 and thus acts to prevent cellular proliferation by preventing G1 to S phase progression of the cell cycle. Please see Section 2.1 for a detailed description of the pathway on which palbociclib acts.

4.4.2 Pharmacodynamics

Palbociclib exhibited half maximal inhibitory concentration (IC_{50}) for CDK4 at 11nM and CDK6 at 15nM. Palbociclib was studied in multiple cell-line panels. Specifically palbociclib treatment demonstrated inhibition of cell proliferation in breast carcinoma cells with an IC_{50} of 0.032 μM. In cell lines without expression of Rb, palbociclib did not have an antiproliferative activity when assayed at concentrations up to 3 mM. The combination of palbociclib with tamoxifen or fulvestrant resulted in an additive inhibition on cell viability in hormone receptor positive breast cancer cell lines. The combination of palbociclib and letrozole (at 40 nM) provided an additional inhibition of cell proliferation of 39% in estrogen receptor positive cell lines. The addition of palbociclib to letrozole in an estrogen-dependent patient derived xenograft breast cancer model was shown to have result in decreased tumor growth compared to placebo or compared to either drug given individually.

4.4.3 Pharmacokinetics

The pharmacokinetics of palbociclib were characterized in patients with solid tumors including advanced breast cancer and in healthy subjects.

Absorption

The mean Cmax of palbociclib is generally observed between 6 to 12 hours (time to reach maximum concentration, Tmax) following oral administration. The mean absolute bioavailability of palbociclib after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and Cmax increased proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulated with a median accumulation ratio of 2.4 (range 1.5-4.2).

Food effect:

Palbociclib should be administered with food. A bioequivalence trial showed that the commercial freebase formulation was not bioequivalent to the isethionalte salt formulation used in the pivotal trial A5481003 under overnight fasted conditions. Therefore, the applicant conducted a comparative bioavailability trial which showed that the exposure of the commercial freebase formulation administered with food was comparable to the isethionate salt formulation used in trial A5481003, administered under a modified fasted condition similar to trial A5481003.

Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Therefore, food intake reduced the intersubject variability of palbociclib exposure, which supports administration of palbociclib with food. Compared to palbociclib given under overnight fasted conditions, the population average AUCinf and Cmax of palbociclib increased by 21% and 38% when given with high-fat food (high-calorie (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate and fat, respectively), by 12% and 27% when given with low-fat food (approximately 400 to 500 calories with 120, 250, and 28 to 35 calories from protein, carbohydrate and fat, respectively), and by 13% and 24% when moderate-fat food (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate and fat, respectively) was given 1 hour before and 2 hours after palbociclib dosing.

As a result, food intake reduced the inter-subject variability in palbociclib exposure for the commercial freebase formulation, compared to the overnight fasted condition, which supports the recommended administration of palbociclib with food.

Distribution

Binding of palbociclib to human plasma proteins in vitro was approximately 85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The geometric mean apparent volume of distribution (Vz/F) was 2583 L (26% CV).

Metabolism

In vitro and in vivo studies indicated that palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [14C]palbociclib to humans, the major primary metabolic pathways for palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma (23%). The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1.5% of the administered dose in the excreta. Palbociclib was extensively metabolized with unchanged drug accounting for 2.3% and 6.9% of radioactivity in feces and urine, respectively. In feces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 26% of the administered dose. In vitro studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulfotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Elimination

The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.1 L/hr (29% CV), and the mean (± standard deviation) plasma elimination half-life was 29 (±5) hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [14C]palbociclib, a median of 91.6% of the total administered radioactive dose was recovered in 15 days; feces (74.1% of dose) was the major route of excretion, with 17.5% of the dose recovered in urine. The majority of the material was excreted as metabolites.

Pharmacokinetics in Special Populations

Hepatic Impairment

Based on a population pharmacokinetic analysis that included 183 patients with cancer, where 40 patients had mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Renal Impairment

Based on a population pharmacokinetic analysis that included 183 patients with cancer, where 73 patients had mild renal impairment (60 mL/min ≤ CrCl <90 mL/min) and

29 patients had moderate renal impairment (30 mL/min ≤ CrCl <60 mL/min), mild and moderate renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients with severe renal impairment.

Age, Gender, and Body Weight

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age range from 22 to 89 years, and body weight range from 37.9 to 123 kg), sex had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

Drug Interactions

In vitro data indicate that CYP3A and sulfotransferase (SULT) enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

CYP3A Inhibitors: Data from a drug interaction trial (N=12) in healthy subjects indicate that coadministration of multiple 200-mg daily doses of itraconazole with a single 125-mg palbociclib dose increased palbociclib AUCinf and the Cmax by approximately 87% and 34%, respectively, relative to a single 125-mg palbociclib dose given alone.

CYP3A Inducers: Data from a drug interaction trial in healthy subjects (N=14) indicated that coadministration of multiple 600-mg daily doses of rifampin with a single 125 mg palbociclib dose decreased palbociclib AUCinf and the Cmax by 85% and 70%, respectively, relative to a single 125 mg palbociclib dose given alone.

CYP3A Substrates: Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In a drug interaction trial in healthy subjects (N=26), coadministration of midazolam with multiple doses of palbociclib increased the midazolam AUCinf and the Cmax values by 61% and 37%, respectively, as compared with administration of midazolam alone.

Gastric pH Elevating Medications: In a drug interaction trial in healthy subjects, coadministration of a single 125 mg dose of palbociclib with multiple doses of the PPI rabeprazole under fed conditions decreased palbociclib Cmax by 41%, but had limited impact on AUCinf (13% decrease), when compared to a single dose of palbociclib administered alone. Given the reduced effect on gastric pH of H2-receptor antagonists 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. In another healthy subject study, coadministration of a single dose of palbociclib with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUCinf and Cmax by 62% and 80%, respectively, when compared to a single dose of palbociclib administered alone.

Letrozole: Data from a drug interaction trial in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the two drugs were coadministered.

Effect of Palbociclib on Transporters: In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2 and organic anion transporting polypeptide (OATP)1B1, OATP1B3 at clinically relevant concentrations.

Effect of Transporters on Palbociclib: Based on in vitro data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of palbociclib at therapeutic doses.

Coadministration of midazolam with multiple doses of palbociclib increased the midazolam AUC by 61%, in healthy subjects, compared with administration of midazolam alone. Therefore, concomitant use of sensitive CYP3A substrate drugs with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) (b) (4) palbociclib may increase their exposure. If coadministration of palbociclib with a sensitive CYP3A substrate drug with a narrow therapeutic index cannot be avoided, the dose of the sensitive CYP3A substrate may need to be reduced.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Data from 18 studies were submitted to the NDA. This included the pivotal Phase 1/2 study (PALOMA-1/A5481003), the confirmatory Phase 3 study (PALOMA-2/A5481008), and two other clinical studies (A5481023, A5481004). Additional studies submitted included two bioavailability (BA) studies (A5481015, A5481021), four comparative BA and bioequivalence (BE) studies (A5481009, A5481020, A5481022, A5481036), three PK and tolerability studies (A5481011, A5481001, A5481010), four extrinsic factor PK studies (A5481012, A5481017, A5481018, A5481026) and a patient PD and PK/PD study (A5481002).

For the purpose of this review, the key clinical study is the randomized Phase 2 portion of PALOMA-1, Study A5481003 (shown in Table 4).

Table 4: Key Clinical Study Submitted

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoint	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
A5481003	Phase 1/2 randomized open-label study to assess the efficacy, safety and pharmaco-kinetics of palbociclib in combination with letrozole	Palbociclib 125mg daily for 3 weeks on 1 week off with letrozole 2.5mg daily vs. letrozole 2.5mg daily	Phase 1: RP2D Phase 2: PFS	Median days on treatment Phase 2: palbociclib-420, letrozole 428 vs letrozole 231	177 Phase 1 =12 Phase 2 =165	First Line Advanced Breast Cancer, Postmeno-pausal, HR+, HER2-	Phase 1: 3 centers in US Phase 2: 12 countries with 50 centers

RP2D: recommended phase 2 dose
Source: PALOMA-1 Protocol

5.2 Review Strategy

The clinical review is based on the clinical study report for the randomized Phase 2 portion of the pivotal study PALOMA-1, A5481003. The efficacy review was conducted by Dr. Julia Beaver and the safety review by Dr. Laleh Amiri-Kordestani. A statistical review was conducted by Dr. Erik Bloomquist. Among the items reviewed were the original electronic submission of the NDA including the Applicant's Clinical Study Report (CSR), the electronic submissions from the applicant in response to clinical and biostatistical queries, case report forms (CRFs), selected narratives, primary data sets for baseline characteristics, efficacy and toxicity submitted by the applicant, research of the FDA data base for regulatory history of the palbociclib IND 69,324 and a literature review of hormone receptor positive metastatic breast cancer and the cyclinD1-CDK pathway. Reproduction/auditing of key efficacy and safety analyses using raw and derived datasets provided by the applicant and performance of sensitivity analysis and exploratory subgroup analyses were performed. JMP® 9.0.2 software was utilized for these analyses. In addition, consultation with other disciplines, including Biostatistics, Clinical Pharmacology, CMC and Toxicology reviewers was undertaken.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Phase 1/2 PALOMA-1 (A5481003)

This NDA submission is primarily supported by results from the randomized Phase 2 portion of a single industry-sponsored study, PALOMA-1 (U.S. study number A5481003), entitled:

> "Phase 1/2, Open-Label, Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole Plus PD 0332991 (Oral CDK 4/6 Inhibitor) and Letrozole Single Agent for the First-Line Treatment of ER Positive, HER2 Negative Advanced Breast Cancer in Postmenopausal Women"

PALOMA-1 Study Design and treatment plan:

The protocol design was a Phase 1/2, randomized, multicenter, international, two-arm, open-label clinical trial designed to compare the safety and efficacy of palbociclib plus letrozole with that of letrozole alone for ER-positive, HER2-negative MBC.

The Phase 1 portion of the study was a limited safety and tolerability study and also served to exclude a pharmacokinetic interaction with the combination of letrozole and palbociclib. Twelve patients were treated to establish the Recommended Phase 2 Dose (RP2D). The review does not focus on this portion of the study.

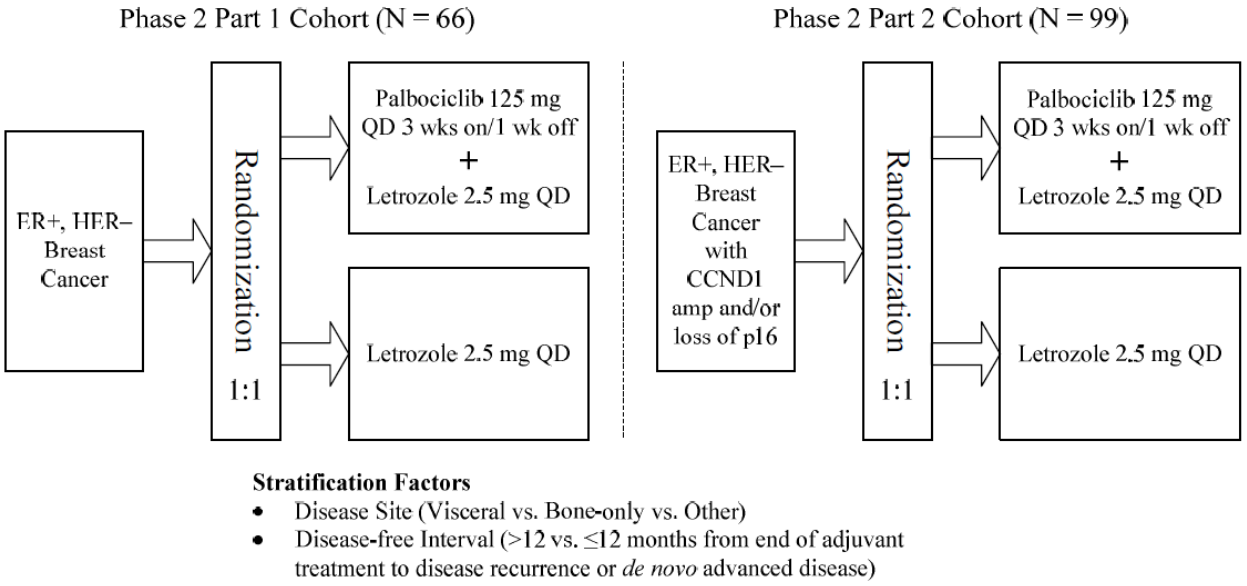
The Phase 2 portion of the study was divided into two parts (schema shown in Figure 2). Part 1 included 66 biomarker-unselected patients randomized to receive palbociclib plus letrozole or letrozole alone in a 1:1 fashion. Part 2 included 99 biomarker-positive (CCND1 gene amplification and/or loss of *CDKN2A*) patients randomized in the same fashion as in Part 1. Enrolment occurred in more than 10 countries worldwide.

- Arm A (experimental arm): Palbociclib 125mg/day orally for 3 weeks followed by 1 week off plus letrozole 2.5mg/day orally
- Arm B (control arm): letrozole 2.5mg/day orally

Randomization occurred based on disease site (visceral vs. bone only vs. other) and by disease-free interval (> 12 months after completion of previous adjuvant treatment vs. $\leq$12 months or de novo disease).

Patients received study treatment until progressive disease (as assessed by the investigator), unmanageable toxicity, or consent withdrawal. Assessment of PFS, the primary objective for this trial, was based on Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0) and was determined by independent review of baseline and follow-up assessments obtained every eight weeks or if progression was expected regardless of study treatment discontinuation.

Figure 2: PALOMA-1 (A5481003) Phase 2 Study Design (Applicant Figure)



Source: CSR p56

Reviewer Comment: *This trial was not originally designed to support registration. Multiple data driven amendments occurred throughout the study as noted below in the "PALOMA-1 Protocol Amendments" Section. Although these changes could have affected the interpretation of the results, multiple sensitivity analyses conducted by the sponsor as well as the FDA review team confirm the improved efficacy findings of palbociclib treatment (see Section 6).*

PALOMA-1 Phase 2 Objectives

Primary Objective

- To assess the effect of palbociclib plus letrozole compared to letrozole alone on progression-free survival (PFS) in the first-line treatment of ER+, HER2 negative Advanced Breast Cancer in postmenopausal women.

Secondary Objectives

- To assess secondary measures of efficacy for palbociclib administered in combination with letrozole and for letrozole alone.
- To assess the safety and tolerability of palbociclib administered in combination with letrozole and of letrozole alone.
- To assess the impact of palbociclib in combination with letrozole and of letrozole alone on patient reported outcomes of pain severity and pain interference with various activities of daily life.
- To explore the relationship between copy number and expression of baseline genes of interest and protein levels including Rb, p16/INK4A, CCND1, CDK4, CDK6, and Ki67 markers with tumor response.

- To explore the relationship between germline polymorphism in CYP19A1 and CCND1 genes and tumor response.

PALOMA-1 Eligibility Criteria

Inclusion Criteria:

Subjects must have met all of the following inclusion criteria to have been eligible for enrollment into the study:

- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of 1) locally recurrent disease not amenable to resection or radiation therapy with curative intent, or 2) metastatic disease.
- ER positive tumor. Positivity is defined either as ≥10 fmol of H3 -estrogen binding per mg of cytosol protein for dextran-coated charcoal and sucrose density methods, or ≥0.10 fmol of H3 -estrogen binding per mg of DNA for IF/EIA technique. In case of use of immunohistochemistry, the report should mention positive receptor status according to the standards of the laboratory.
- HER2 negative breast cancer by FISH or IHC.
- Paraffin-embedded tumor block(s) available for centralized assessment of Rb and other cell cycle-related proteins. Phase 2 Part 2 only: CCND1 amplification and/or loss of p16 as determined by the central laboratory.
- Measurable disease according to RECIST or bone-only disease (Phase 2 only).
- Previously irradiated lesions are deemed measurable only if progression is documented at the site after completion of radiation.
- Females, 18 years of age or older.
- Postmenopausal status defined as:
    - Prior bilateral surgical oophorectomy;
    - Amenorrhea and age ≥60 years;
    - Age <60 years and amenorrhea for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal ranges.
- Eastern Cooperative Oncology Group (ECOG) Performance status 0 or 1 (see Appendix 1).
- Resolution of all acute toxic effects of prior therapy or surgical procedures to CTCAE grade <1 (except alopecia or other toxicities not considered a safety risk for the patient).
- Adequate organ function as defined by the following criteria:
    - Absolute neutrophil count (ANC) ≥1500/μL;
    - Platelets ≥100,000/μL;
    - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤3 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy;

  - Total serum bilirubin ≤1.5 x ULN regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin due to Gilbert's syndrome is permitted;
  - Serum creatinine ≤1.5 x ULN;
  - QTc ≤470 msec (based on the mean value of the triplicate ECGs).
- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
- Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria:

Subjects presenting with any of the following were not to be included in the study:

- Brain metastases (even if treated and stable), spinal cord compression (history or presence of), carcinomatous meningitis, or leptomeningeal disease.
- Major surgery within 3 weeks of first study treatment.
- Prior treatment with:
  - Any anti-cancer therapies for advanced disease, with the exception of radiation therapy to <25% of bone marrow at least 2 weeks prior to study treatment initiation (see Appendix 2);
  - (neo)adjuvant letrozole with disease recurrence ≤12 months (Phase 2 only);
  - Any CDK inhibitor.
- Current treatment with:
  - Any anti-cancer therapies for advanced disease;
  - Any experimental treatment on another clinical trial;
  - Therapeutic doses of anticoagulant. Low dose anticoagulants for deep vein thrombosis prophylaxis are allowed. Low molecular weight heparin is allowed. Aspirin is permitted.
- Current use or anticipated need for:
  - food or drugs that are known strong CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, posaconazole, erythromycin, clarithromycin, tilithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, nefazodone, diltiazem, and delavirdine) – for both Phases 1 and 2;
  - drugs that are known strong CYP3A4 inducers (ie, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's Wort) – for Phase 1 only.
- Diagnosis of any secondary malignancy within the last 3 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

- Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE 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.
- Active inflammatory bowel disease or chronic diarrhea. Short bowel syndrome. Upper gastrointestinal surgery including gastric resection.
- Known hypersensitivity to letrozole or to any of its excipients.
- Known human immunodeficiency virus infection.
- 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 subject inappropriate for entry into this study.

Palbociclib Formulation and Packaging:

Palbociclib is formulated in (b) (4) capsules containing 25 mg or 100 mg of study medication. Medication was provided in non-patient specific bottles containing either 25 mg or 100 mg capsules.

Letrozole Formulation and Packaging:

Letrozole (FEMARA®) is commercially available as film-coated tablets. Each tablet contains 2.5 mg letrozole as active ingredient.

Rationale for Dose Selection:

Based on clinical results for safety and toxicity from prior studies 1001 and 1002 the recommended dose of palbociclib was deemed to be 125mg/day. The Phase 1 portion of the study determined the RP2D in combination with letrozole (2.5mg/day) as 125mg/day given for three weeks with one week off. The approved letrozole dose for this indication is 2.5mg/day and thus that was used in both study arms.

Palbociclib Drug Administration:

Patients were instructed to swallow the study medication whole and not chew the capsule prior to swallowing. Patients were instructed to take their dose at approximately the same time each day. If a patient missed a day's dose entirely, they were instructed not to "make it up" the next day by taking an extra dose. If a patient inadvertently took 1 extra dose during a day, the patient was not to take the next day's dose of palbociclib. Patients in the Phase 2 study were to be fasted from 1 hour before to 2 hours after palbociclib dosing.

Reviewer Comment: *Initially there was no instruction for fasting or fed state; Amendment 2 (July 2009) indicated the need for fasting state. The Phase 3 confirmatory study PALOMA-2 requires a fed state due to bioequivalence issues with the formulation (see Section 4.4.3, Clinical Pharmacology review, and CMC review). The formulation used in the Phase 3 study will be the formulation marketed if this application receives accelerated approval.*

Dose Delay and Modification of Palbociclib:

Palbociclib was to be adjusted for toxicity as described in Table 5 and 6. Patients requiring more than two dose reductions were to be discontinued from the study. A new cycle of treatment with palbociclib could only begin if patients had an ANC ≥1,000/μL, Platelets ≥50,000/μL and their non-hematologic toxicities had returned to baseline or Grade ≤1 severity (or Grade ≤ 2 at the investigator discretion if not considered a safety risk). If these conditions were not reached letrozole could be continued and palbociclib delayed by one week. If after this delay all toxicities had recovered to the criteria above then palbociclib could be resumed. If the patient did not recover after 2 weeks (including the scheduled 1-week off treatment period within a cycle) treatment with palbociclib was permanently discontinued.

Table 5: Dose Levels (Applicant Table)

Dose Level	PD 0332991 for 3 out of 4 weeks (3/1 schedule)	Letrozole on a continuous regimen
1	125 mg/d	2.5 mg/d
-1	100 mg/d	2.5 mg/d
-2	75 mg/d*	2.5 mg/d

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

Source: protocol A5481003 p553

Table 6: Recommended Palbociclib Dose Modifications Based on Treatment-Related Toxicity in the Prior Cycle (Applicant Table)

Worst Toxicity During Previous Cycle	New Cycle
Grade 4 neutropenia	↓ 1 Dose Level
Grade 4 thrombocytopenia	↓ 1 Dose Level
Grade 3 neutropenia associated with a documented infection or fever ≥38.5°C	↓ 1 Dose Level
Grade ≥3 non-hematologic toxicity (includes nausea, vomiting, diarrhea, and hypertension only if persisting despite maximal medical treatment)	↓ 1 Dose Level
Delay by >1 week in receiving the next scheduled dose of either study treatment due to persisting treatment-related toxicities (platelet count <50,000/μL; ANC <1,000/μL; nonhematologic toxicities of Grade ≥3 severity). (Phase 1 only)	If recovery occurs within a maximum of 2 weeks, continue and ↓ 1 Dose Level
Inability to deliver at least 80% of the planned PD 0332991 or letrozole doses during Cycle 2 due to adverse events possibly related to study treatment (Phase 1 only)	↓ 1 Dose Level

Source: protocol A5481003 p554

Dose Delay and Modification of letrozole:

No dose adjustment was permitted for letrozole; interruptions were allowed.

Concomitant Medications:

Medications taken by the patient during the trial were to be recorded on the CRF. CYP3A isoenzyme inhibitors or inducers were not permitted during the study. While no additional anticancer therapy was permitted, patients were allowed to continue bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors if they were receiving them at the time of study entry. If patients required initiation of these bone modulating agents the investigator had to consult with the applicant and confirm that the treatment was not indicative of disease progression. Prophylactic use of granulocyte-colony stimulating factors was not permitted but use was allowed if treatment-emergent neutropenia was experienced as indicated by current guidelines. If neutropenic complications were observed in a cycle, the protocol allowed secondary prophylaxis at the discretion of the investigator if dose reduction or delay were not options. Erythropoietin was also allowed at the investigators discretion.

Concomitant Radiation or Surgery:

Palliative radiotherapy was permitted for the treatment of painful bony lesions as long as the lesions were known to be present at the time of study entry and the investigator did not believe the need for radiation indicated disease progression. Surgeries were allowed during treatment with caution advised.

Reviewer Comment: *Radiation or surgery could be problematic if palliative radiotherapy or surgery were performed on the only site of metastatic disease (see Section 6.1.3).*

Safety and Efficacy Assessments:

Assessments of adverse events included type, incidence, severity (graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 2.0), timing, seriousness, and relatedness. Disease assessment at screening included physical exam, CT or MRI scans (chest, abdomen and pelvis), and x-rays for bone lesions (if applicable) within 4 weeks of start of treatment. Subsequent assessments were performed every 8 weeks until disease progression or a patient begins a subsequent anticancer therapy independent of discontinuation of palbociclib. Bone scans were carried out at baseline and every 12 weeks thereafter or if suspicion of new lesions. See Table 7 for full details of study assessments.

Table 7: PALOMA-1 Phase 2 Schedule of Assessments (Applicant Table)

Protocol Activities	Screening	Study Treatment[1]			End of Treatment	
		Cycles 1 and 2		Cycles ≥3		
	≤28 Days Prior to Dosing	Day 1 (±1)[2]	Day 14 (±1)	Day 1 (±2; ±7 for imaging)	End of Txt / Withdrawal[3]	Post Txt Follow-up[20]
Baseline Documentation						
Informed Consent[4]	X					
Medical/ Oncological History[5]	X					
Baseline Signs/Symptoms		X				
Tumor Tissue and Blood Samples for Molecular Biomarkers and Patient Selection[6]	X					
Physical Examination[7]	X	X		X	X	
ECOG Performance Status	X	X		X	X	
Laboratory Studies						
Hematology[8]	X	X	X	X	X	
Blood Chemistry[8]	X	X	X	X	X	
12-lead ECG[9]	X	X	X	X (Cycle 3)	X	
Disease Assessments						
CT or MRI Scans of Chest, Abdomen, Pelvis; X-ray Scans of Bone Lesions; and Clinical Evaluation of Superficial Disease [10]	X		End of Cycle 2 (Day 28 ±7)	X (Every other cycle starting from end of Cycle 4)	X	
Brain CT or MRI Scan[11]	(X)					
Bone Scan[12]	X			X (Every 12 weeks	X	
Other Clinical Assessments						
Drug Compliance[13]			X		X	
Adverse Events[14]	X	X	X	X	X	X
Concomitant Medications/Treatments[15]	X	X	X	X	X	X
mBPI-sf Pain Assessment[16]		X		X	X	
Survival Follow-up[17]						X

Protocol Activities	Screening	Study Treatment[1]			End of Treatment	
		Cycles 1 and 2		Cycles ≥3		
	≤28 Days Prior to Dosing	Day 1 (±1)[2]	Day 14 (±1)	Day 1 (±2; ±7 for imaging)	End of Txt / Withdrawal[3]	Post Txt Follow-up[20]
Study Treatment						
Randomization	X					
PD 0332991 (Arm A only)		Daily for 21: 28 days				
Letrozole (Arm A and Arm B)		Daily				
Special Laboratory Studies						
Pharmacokinetics (Arm A only)[18]			X		X	
Sample Banking for Exploratory Research (Optional)[19]	X					

( ) – if applicable

Footnotes for Schedule of Activities – Phase 2	
1.	**Study Treatment:** All assessments should be performed prior to dosing with study medications unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings.
2.	**Cycle 1/Day 1:** Blood chemistry, hematology, and physical examination not required if acceptable screening assessment is performed within 7 days prior to the start of study treatment
3.	**End of Treatment/Withdrawal:** Obtain these assessments if not completed during the previous 4 weeks on study (during the last 8 weeks on study for disease assessments or the last 3 months for bone scans), with the exception of the plasma sample for PD 0332991 and letrozole concentrations.
4.	**Informed Consent:** Must be obtained prior to undergoing any trial specific procedure.
5.	**Medical/Oncological History:** To include information on prior regimens.
6.	**Tumor Tissue and Blood Samples for Molecular Biomarkers and Patient Selection:** Part 1 and Part 2 Molecular Biomarkers (all patients): Paraffin block(s) of adequate size to allow for three 0.6 x 5 mm deep punches for a tissue microarray. If no block is available, at least 10 glass slides, each containing an unstained 5-micron thick tissue section, are acceptable. Archived or fresh tumor samples acceptable. Blood sample: one 2 mL blood sample. Part 1 Optional Molecular Biomarkers: In addition to the required tumor tissue sample outlined above, additional 10 slides (if no block is available) will be sent to a central laboratory for the retrospective assessment of biomarkers (CCND1 amplification and/or loss of p16) on an optional basis. Part 2 Patient Selection Biomarkers: Tumor block(s) or 10 slides (if no block is available) for patient selection markers will be sent to a central laboratory for the assessment of biomarkers (CCND1 amplification and/or loss of p16) before the patient is eligible for full screening. This patient selection assessment can be evaluated outside the 28-day screening window, and the results must be obtained prior to proceeding to other screening procedures. Tissue samples from all screened patients, including those that are found to be negative for the patient selection biomarkers, will be used for additional analyses, including further evaluation of a potential companion diagnostic test. For patients who are determined to be negative for the patient selection biomarker and who will therefore not be enrolled into the study, no more than 10 slides total, either sent by the sites or sectioned from a submitted tissue block, will be used for these analyses, and tissue blocks will be returned to site immediately after assessment of the patient selection biomarker.
7.	**Physical Examination:** includes an examination of major body systems (at screening and on Day 1 of each cycle), height (at screening only); weight, blood pressure and pulse rate (on Day 1 of each cycle).
8.	**Hematology and Blood Chemistry**: Hematology includes hemoglobin, WBC, neutrophils, lymphocytes, platelet count. Blood chemistry includes BUN (or urea), creatinine, albumin, AST/ALT, total bilirubin, alkaline phosphatase, LDH, sodium, potassium, calcium, magnesium, phosphorous, uric acid. Additional hematology/chemistries may be performed as clinically indicated.

Footnotes for Schedule of Activities – Phase 2	
9.	**12-lead ECG**: At each time-point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTc interval. **Arm A:** To be performed on Day 1 of Cycles 1 and 3; and on Day 14 of Cycles 1 and 2, the ECGs should be performed in the morning and time matched (±1 hour) with the pre-dose PK samples when applicable. **Arm B:** To be performed on Day 1 of Cycles 1, 2, and 3. If the mean QTc interval is prolonged (>500 msec), then the ECGs should be re-evaluated by a qualified person at the center for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
10.	**Tumor Imaging:** Disease assessment should be performed as outlined in the assessment table, whenever disease progression is suspected, and to confirm a partial or complete response (at least 4 weeks after initial documentation of response). Disease assessment at screening will include CT or MRI scan of the chest, abdomen, and pelvis (CAP), X-rays for bone lesions (if applicable), and clinical assessment of superficial disease. Assessments will be performed at screening and at 8-week intervals until disease progression has been documented or the patient begins a subsequent anticancer therapy, regardless of study treatment discontinuation. The schedule of assessments should be fixed according to the calendar, regardless of treatment delays.
11.	**Brain CT or MRI Scan:** Baseline brain scans are only required in case signs and symptoms suggest presence of metastatic brain disease. Post screening repeat brain scans will be required only if metastases are suspected.
12.	**Bone Scan:** Bone scans are required at baseline. Baseline lesions will be followed up with the most appropriate imaging technique. Bone scans will be repeated at 12-week intervals, or when new bone metastases are suspected. A bone scan is required at the time of confirmation of CR for subjects who have bone metastases.
13.	**Drug Compliance:** PD 0332991 and letrozole bottle(s)/blisters including any unused capsules/tablets will be returned to the clinic for drug accountability.
14.	**Adverse Events:** Refer to Adverse Event Reporting section.
15.	**Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.
16.	**PRO Pain Assessment (mBPI-sf):** Patients will complete questionnaires at the clinic prior to any study or medical procedure. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home.
17.	**Survival Follow-Up:** After discontinuation of study treatment, post-study survival status (including post-study anticancer therapies) will be collected every 2 months until death. Telephone contact is acceptable.
18.	**Pharmacokinetics (Arm A only):** For PD 0332991, plasma samples will be collected pre-dose (time matched to ECGs) and another sample between 1 to 8 hours after dosing on Day 14 of Cycles 1 and 2. Samples for PD 0332991 will be collected also at End of Treatment. At each sampling time-point, 3 mL of blood will be drawn into EDTA tubes. Plasma PK samples must be drawn after any matched ECG assessment such that samples are collected at nominal time. The PK sample collection for PD 0332991 may be repeated during a later cycle, if the sample collection is missed for any reason or if the PK data collected are deemed inevaluable by the Sponsor. The PK samples may only be repeated for the patients if they have not been dose reduced.
19.	**Sample Banking for Exploratory Research (Optional)**: this component is optional and subject to IRB/EC approval. In consenting patients, two de-identified blood samples (a 9 mL sample for genotyping and a 2.5 mL sample for RNA transcript profiling) will be collected, together with de-identified tumor sections from archived formalin-fixed paraffin embedded tumor tissue. (Please refer to molecular profiling supplement for additional details).
20.	**Post Txt Follow-up:** Complete follow-up visit approximately 28 days after last dose of study treatment.

Source: protocol A5481003 p528-530

Biomarker Assessment:

Tumor tissue samples were used for both Part 1 and Part 2 of the Phase 2 study. Paraffin blocks or 10 glass slides of fresh or archived tumor samples were obtained. For Part 2 the tissue samples were prospectively sent to a central laboratory for the assessment of CCND1 amplification and p16 loss. For Part 1, the assessment of biomarkers was performed retrospectively for all available samples.

CCND1 amplification was determined by fluorescence in situ hybridization (FISH) analysis with amplification determined by a CCND1/CEP11 ratio ≥1.5. CDKN2A/p16^{INK4A} (*CDKN2A*) gene loss was determined by a CDKN2A/CEP9 ratio <0.8 by FISH analysis. A patient was deemed biomarker-positive if they were found to have the following profile by FISH analysis:

- ≥1.5 ratio for CCND1/cep11 and/or
- <0.8 ratio for CDKN2A/cep9

Part 2 screened 319 patients with 99 patients testing as biomarker positive.

Reviewer Comment: *It is important to note that the cut off for CCND1 expression is a very inclusive value for CCND1 amplification and thus captured a large percentage of screened patients. Please see Section 6.1.6 and 6.1.8 for a detailed discussion of the relevance of the biomarker population in this study.*

PALOMA-1 (A5481003) Phase 2 Study Endpoints

Primary Endpoint:

- The primary efficacy endpoint of PFS, based on investigator assessment, is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

  PFS (days) = [date of progression or date of death on study or censoring- date of randomization +1]

  Documentation of progression was by objective disease assessment as defined by the Response Evaluation Criteria in Solid Tumors (RECIST).

Secondary Endpoints:

- Objective Response (OR)
- Clinical Benefit Rate (CBR)
- Time to Tumor Progression (TTP)
- Duration of response (DR)
- Overall Survival (OS): the time for randomization date to date of death due to any cause
- Overall Safety Profile
- Patient Reported Outcome (PRO) of pain using the modified Brief Pain Inventory-short form (mBPI-sf).
- Tumor tissue levels including but not limited to Rb, p16/INK4A, CCND1, CDK4, CKD6, and Ki67 and copy number of CCND1 and p16
- Germline polymorphism in CYP19A1 and CCND1 genes

Reviewer Comment: *The PFS endpoint is a common endpoint in oncology trials and has been used to support both accelerated and full approval in various malignancies. The confirmatory study PALOMA-2 also has PFS as its primary endpoint. It is difficult to detect an OS benefit in the proposed indication where patients will be treated with multiple subsequent lines of therapy.*

Sample Size Determination:
The randomized Phase 2 study as previously mentioned was divided into two parts. Initially prior to the addition of the Part 2 biomarker enriched population the study was meant to enroll 150 unselected patients, however enrollment to this cohort was stopped at 66 patients. Part 2 of the study was designed to enroll 150 patients (75 per treatment arm) over 13 months as determined by the primary endpoint of PFS. Assuming a PFS of 9 months for the control treatment arm and a 50% improvement in the combination arm, 114 PFS events were anticipated to be observed for a total follow-up time of 30 months. Under the alternate hypothesis with a 1-sided alpha = 0.10, there was 80% power to detect a hazard ratio of 0.67 assuming one futility interim analysis. However an adjustment was made based on data from the interim analyses (the first performed at

28% of information and 31 PFS events and the second at 50% of information and 57 PFS events) demonstrating a lower event rate and a larger effect size in both the biomarker enriched and the unselected population. Therefore the final analysis of PFS was changed to occur when 95 PFS events had accumulated. At 95 PFS events, there would be more than 98% power to detect a hazard ratio of 0.50 at 1-sided alpha = 0.10 or 75% power to detect a hazard ratio of 0.67. In the Part 2 portion it was estimated that 50 PFS events would be observed at the time of final analysis.

Efficacy Analysis Populations:
Primary Analysis Set (Intent To Treat [ITT]): All randomized patients from the Phase 2 study (both Part 1 and Part 2) as randomized regardless of what treatment, if any, was received. Patients not enrolled or randomized (screened only patients) were not included in any analysis.

Similar to the Primary Analysis Set, each Part of the Phase 2 study was independently analyzed as their respective ITT populations: all randomized patients from Part 1 where patients are classified according to the randomized treatment regardless of what treatment, if any, was received and all randomized patients from Part 2 where patients are classified according to the randomized treatment regardless of what treatment, if any, was received. For objective response only randomized patients with measurable disease at baseline were included. For duration of response only responders were to be included.

Safety Analysis Population:
Patients who received at least one dose of study medication (based on the treatment they actually received) were to be included in the safety analyses.

Protocol Deviations:
Major deviations were defined as having been treated according to the other treatment arm. Patients not treated with one of the treatments were excluded from the safety analysis. Other deviations did not exclude patients from the analysis.

Handling of Missing Values:
If a day is missing the 1st of the month was used to replace the missing date. If baseline tumor assessment is lacking the patient were considered indeterminate (IND) and PFS data was censored. If measurements for one or more target lesions were missing the status for the evaluation was indeterminate. Missing non-target disease assessment generally did not affect response determination except if CR then the patient was deemed partial response.

Efficacy Analysis:
The protocol specified primary efficacy analyses were based on investigator assessment of progression and response. Additional analyses based on BICR were considered secondary analyses. The primary analysis population was all randomized patients from the Phase 2 study (both Part 1 and Part 2 combined). This analysis population was the intention to treat (ITT) population. The critical value that was utilized

to determine statistical significance at the time of the final analysis was based on the actual number of events observed and the α spent in the two interim analyses. Efficacy analyses for the Phase 2 study are summarized in Table 8. The null hypothesis was that the addition of palbociclib had no treatment effect. At the final PFS analysis a gate-keeping procedure was used for hypotheses testing in a hierarchical approach to control the family-wise error rate. The testing started with the combined patient population from Part 1 and Part 2. If unable to reject the null hypothesis based on the combined population a Holm procedure was used to test Part 1 and Part 2 as individual cohorts. If the null hypothesis was rejected, the same hypotheses was tested for Part 1 and Part 2 as two cohorts separately at the next level with the same significant level α as used for the previous testing.

The significance level for the final analysis was to be adjusted for the two interim analyses. PFS for the palbociclib plus letrozole and letrozole alone arm was assessed using Kaplan-Meier (KM) methods and displayed graphically with median event times and confidence intervals. In addition, the difference in PFS between the treatment and control arms was analyzed using a stratified log-rank test. Unstratified log-rank test was to be applied as a sensitivity analysis and cox regression models were used to estimate the treatment hazard ratio and the confidence intervals.

Subgroup analyses of PFS based on the investigator assessment were to beperformed for the baseline stratification factors, baseline patient characteristics and selected biomarkers.

Table 8: Summary of Key Efficacy Analyses for Phase 2

Endpoint	Analysis Set	Statistical Method	Missing Data	Interpretation
PFS	ITT (P1+P2) Investigator assessment	Stratified log-rank test (all S factors, 1 sided, α=0.10), K-M method (median and 80% & 95% CIs)	Censor Patients on the day following the date of the last tumor assessment	Primary Analysis
PFS	ITT (P1, P2) Investigator assessment	Unstratified log-rank test (1-sided, α =0.10), K-M method (median and 80% & 95% CIs)	Same as the primary analysis	Secondary Analysis
PFS	ITT (P1+P2) BICR	Stratified log-rank test (Part only, 1-sided, α =0.10) K-M method (median and 80% & 95% CIs)	Same as the primary analysis	Secondary Analysis
	ITT (P1, P2) BICR	Unstratified log-rank test (1-sided, α =0.10), K-M method (median and 80% & 95% CIs)		

Source: Adapted from Applicant SAP page 45, Table 8.3

Censoring:
The protocol stated that censoring for the PFS endpoint was to be performed according to the following rules described below and shown in Table 9. Patients last known to be 1) alive, 2) on treatment or within 28 days of discontinuation of treatment, and 3) progression-free, were to be censored at the date of the last objective disease assessment that verified lack of disease progression.

- Patients with inadequate baseline disease assessment were censored at the randomization date.
- Patients with no on-study disease assessments were censored at the randomization date unless death occurred prior to the first planned assessment (in which case the death was an event).
- Patients with at least one on-study disease assessment who discontinue treatment without documented disease progression and without death were censored at the date of the last objective disease assessment documenting no progression (objective status Complete Response (CR), Partial response or Stable Disease/No Response (SD)) prior to 28 days after discontinuation of treatment.

- There were two exceptions. If objective progression or death was documented within 28 days after discontinuation of treatment the progression or death is an event. If a new anti-cancer treatment (including surgery) was started prior to progression and prior to 28 days after discontinuation of treatment, then censorship was at the date of the last objective disease assessment that verified lack of disease progression prior to the new treatment.
- Patients with documentation of progression or death after an unacceptably long interval (>2 consecutive assessments) since the last tumor assessment were censored at the time of last objective assessment documenting no progression.

Table 9: Rules for Determining PFS Status and Date (Applicant Table)

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	Randomization date (Day 1)	Censored
No on-study assessments	Randomization date (Day 1)	Censored
Alive, on treatment[2] and no Progression	Date of last objective tumor assessment documenting no progression	Censored
Progression Documented on or between scheduled tumor assessments prior to treatment discontinuation[2]	Date of first objective tumor assessment documenting objective progression	Progressed (Event)
Treatment discontinuation for undocumented progression	Date of last objective tumor assessment documenting no progression prior to discontinuation[2]	Censored
Treatment discontinuation due to toxicity or other reason	Date of last objective tumor assessment documenting no progression prior to discontinuation[2]	Censored
New anti-cancer treatment (including surgery) <28 days after discontinuation of treatment without progression	Date of last objective tumor assessment documenting no progression prior to new anti-cancer treatment	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation[2]	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments	Date of last objective tumor assessment documenting no progression prior to the event	Censored

Source SAP p61-62

Reviewer Comment: *An independent central review of PFS was not planned in the protocol. This review was performed by Pfizer per FDA recommendation at the End Of Phase 2 Meeting in October 2012.*

Sensitivity Analyses:
Seven pre-specified sensitivity analyses were planed (see Table 10 for definitions). Specifically, censoring rule variations and the effect of various windowing of the timing of the progression assessment were investigated. Additional sensitivity analyses were performed after discussion with the FDA and are described in Section 6.1.5.

Table 10: Sensitivity Analyses

Sensitivity Analysis	Endpoint	Analysis Set	Statistical Method	Missing Data
1	PFS	ITT (P1+P2) Investigator assessment	Unstratified log-rank test (1-sided, α=0.10) K-M method (median and 80% & 95% CIs)	same as the primary analysis
2	PFS	ITT (P1+P2) Investigator assessment	Stratified log-rank test (all S factors per CRF, 1-sided, α =0.10) K-M method (median and 80% & 95% CIs)	same as the primary analysis
3	PFS	ITT (P1+P2) Investigator assessment	Stratified log-rank test (Part only, 1-sided, α =0.10) K-M method (median and 80% & 95% CIs)	different censoring rule (incorporate symptomatic deterioration as event)
		ITT (P1, P2) Investigator assessment	Unstratified log-rank test (1-sided, α =0.10), K-M method (median and 80% & 95% CIs)	
4	PFS	ITT (P1+P2) Investigator assessment	Stratified log-rank test (Part only, 1-sided, α =0.10) K-M method (median and 80% & 95% CIs)	different censoring rule (event can be at post 28 days of treatment discontinuation)
		ITT (P1, P2) Investigator assessment	Unstratified log-rank test (1-sided, α =0.10), K-M method (median and 80% & 95% CIs)	

Table 11: Sensitivity Analyses (Continued)

Sensitivity Analysis	Endpoint	Analysis Set	Statistical Method	Missing Data
5	PFS	ITT (P1+P2) Investigator assessment	Stratified log-rank test (Part only, 1-sided, α =0.10) K-M method (median and 80% & 95% CIs)	different censoring rule (disease progression can only be at the scheduled assessment time)
		ITT (P1, P2) Investigator assessment	Unstratified log-rank test (1-sided, α =0.10), K-M method (median and 80% & 95% CIs)	
6	PFS	AT[1] (P1+P2) Investigator assessment	Stratified log-rank test (Part only, 1-sided, α =0.10) K-M method (median and 80% & 95% CIs)	same as primary analysis
		AT[1] (P1, P2) Investigator assessment	Unstratified log-rank test (1-sided, α =0.10), K-M method (median and 80% & 95% CIs)	
7	PFS with disease, baseline and demographic characteristics as covariates	ITT[1] (P1+P2) Investigator assessment	Stratified multi-var Cox model (Part only) (HR and 80% & 95% CIs)	same as primary analysis
		ITT[1] (P1, P2) Investigator assessment	Multi-var Cox model (HR and 80% & 95% CIs)	

[1]: All treated as treated set (AT)
Source: Adapted from Applicant SAP page 45, Table 8.3

PALOMA-1 Randomization and Blinding:
For the Phase 2 portion, an interactive web response system (IWRS) was planned to collect patient screening information and randomize eligible patients in a 1:1 ratio by a hierarchical randomization scheme to one of the two treatment arms (palbociclib plus letrozole or letrozole alone). Site of disease (visceral vs. bone only vs. other) and disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence vs ≤12 months from the end of adjuvant treatment to disease recurrence or de novo advanced disease) were used as stratification factors. Visceral refers to lung and/or liver disease +/- other sites. Other refers to bone with other non-visceral disease site or other disease site alone.

The study was open-label and thus the patients and investigators were not blinded. The study team had full access to the data from Phase 2 Part 1 as the study was ongoing until the final amendment at which point results were only reported in the interim analyses. The study team did not have access to aggregate analyses or summaries by treatment arm for Phase 2 Part 2 except at the time of the interim analyses. The results from the interim analyses were reviewed by the study team and reported to the applicant's upper management.

PALOMA-1 Protocol Amendments:

Original Protocol March 27, 2008

Protocol Version a1, 8 May 2009 (Sites 1001, 1002, 1004, 1006, 1020, 1025, and 1045 only):
Only changes to the Phase 1 portion were included in this amendment. The Phase 1 portion of the Study was amended to clarify how many patients were to be enrolled in the dose expansion and drug-drug interaction assessments. Inclusion and Exclusion criteria were also modified in the Phase 1 portion of the study only allowing for enrollment of patients with non-measurable disease and prior treatment with (neo)adjuvant letrozole as well as updating the list of prohibited drugs. A new guideline was added for patients to fast from 1 hour before to 2 hours after palbociclib administration. PK sampling instructions were edited and additional guidance for concomitant medications and surgical procedures occurring during the study were added.

Protocol Version a2, 31 July 2009:
The Phase 1 study was further clarified with regard to number of patients enrolled and eligibility for patients who had non-measurable disease and prior treatment with letrozole in the (neo)adjuvant setting. The Phase 2 study was amended with respect to the PK sample collection, and an exclusion criteria excluding patients who were taking or would need strong CYP3A4 food or drugs. Both Phase 1 and 2 were amended to require fasting for administration of palbociclib and a list of prohibited drugs that interact with CYP3A4 was updated. PK sampling was also clarified and additional guidance was added for concomitant medications and surgical procedures occurring during the study.

Protocol Version a3, 1 July 2010:
This amendment split Phase 1 into 2 parts: Part 1 to include 60 patients randomized in a 1:1 fashion to the two arms and Part 2 to include 150 biomarker-positive (CCND1 gene amplification and/or loss of *CDKN2A*) randomized in the same fashion as Part 1. The primary endpoint for the Phase 2 study was made progression-free survival from Part 2 only. The Phase 2 study was amended to allow for enrollment of patients with prior treatment with (neo)adjuvant letrozole if disease recurrence occurred >12 months. A change to the statistical analysis plan instructed an interim analysis for Part 2 of the study.

Protocol Version a4, 10 August 2011:
Phase 2 Part 2 tumor tissue samples were allowed to be stored for additional analyses. PK time points were edited.

Protocol Version a5, 20 June 2012:
The primary endpoint for the Phase 2 portion was changed from PFS from Part 2 only to PFS from a combination of Part 1 and Part 2. The primary analysis population would therefore include all randomized patients from the Phase 2 study (Part 1 and Part 2). The statistical analysis plan was amended accordingly. The Adverse event reporting was updated to align with recent FDA guidance. Medication errors were changed to be considered adverse events. Tumor assessment imaging scans were no longer required to be submitted to the central imaging lab for review. The formerly planned futility interim analysis for Part 2 Phase 2 was replaced by two or possibly three efficacy interim analyses.

Protocol Version a6, 8 November 2012:

The Phase 2 study was amended to allow for post-study survival status every 2 months until death. Tumor assessment imaging scans were required to be submitted to the central imaging lab for review for all patients in the Phase 2 study (Part 1 and Part 2). Reporting of adverse events were changed to not require reporting of events that were part of the disease under study or caused by subsequent anti-cancer treatments.

Protocol Version a7, 11 July 2013:

The final analysis plan for the primary endpoint of PFS was adjusted to be performed when 95 PFS events were accumulated due to the event rate evaluation being slower than observed. Also a formal hypothesis testing procedure to reflect Part 1 and Part 2 as individual cohorts/studies to be analyzed separately was added. The third interim analysis was removed. Adjustments in various sections were performed to conform to the Pfizer protocol template.

Reviewer Comment: *Amendment 3, 5 and 7 were data driven amendments to the protocol and SAP. Initially the protocol was written to enroll 150 biomarker unselected patients. Amendment 3 (July 2010) split the Phase 2 study into two parts by beginning Part 2 which was planned to be 150 biomarker positive patients. It also allowed for an interim analysis for Part 2. This change was based on pre-clinical data indicating a potential effect in the biomarker enriched population. PFS in Part 2 was to be the primary endpoint. After an interim analysis of the Part 1 data was performed and supported a potential benefit in the biomarker unselected population as well as better efficacy than hypothesized, amendment 5 (June 2012) halted enrollment to the Part 2 program and the primary endpoint was changed to include all of the Phase 2 study (Part 1 and Part 2 together). Additionally, amendment 5 replaced the formerly planned futility interim analysis with two or possibly three efficacy interim analyses. Amendment 7 (July 2013) adjusted the final analysis plan for the primary endpoint of PFS to be performed when 95 PFS event accumulated. The option for third interim analysis was removed. It*

is important to note that this trial was not initiated to be a registration trial and many data driven changes were incorporated as the trial was ongoing. It is possible these data driven changes affected the quality of the study and the integrity of the data.

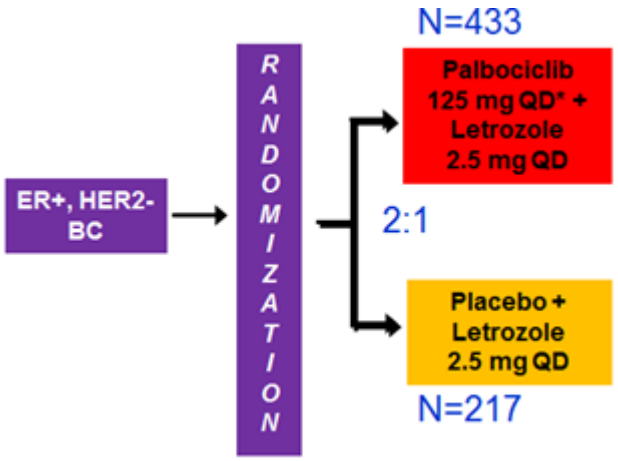
5.3.2 Phase 3 PALOMA-2 (A5481008)

The PALOMA-2 Trial (U.S. study number A5481008) is currently ongoing and is the confirmatory trial for PALOMA-1. PALOMA-2 is entitled:

> "A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease".

PALOMA-2 (A5481008) is a Phase 3, randomized, multicenter, international, double-blind trial designed to confirm the findings of PALOMA-1. This trial has fully accrued and randomized 650 patients 2:1 to receive palbociclib plus letrozole or letrozole plus placebo according to the same dosage and schedule as PALOMA-1. The schema is shown in Figure 3.

Figure 3: PALOMA-2 (A5481008) Schema



BC: breast cancer, QD: daily, *3/1 dosing schedule of 21 days on, 7 days off.
Source: Tabular listing of all clinical studies of palbociclib

The key inclusion and exclusion criteria are the same as PALOMA-1. The same stratification factors as PALOMA-1 are used with the addition of prior (neo)adjuvant therapy (hormonal vs. non hormonal). The primary endpoint of investigator-assessed PFS is also the same as PALOMA-1. There is a planned interim analysis at (b) (4) events

with the ability to detect a HR of (b) (4) or smaller which equates to approximately a (b) (4) month difference in median PFS. For the final analysis the study is powered to detect a HR of (b) (4) which equates to approximately a (b) (4) month difference in median PFS.

Interim analysis results are expected in the third or fourth quarter of 2015 at (b) (4) ((b) (4) % of final) events and final analysis at (b) (4) events is expected in the first or second quarter of 2016.

Reviewer Comment: *PALOMA-2 is fully accrued which reassures the review team that the final analysis of this study would not be affected by the marketing of palbociclib.*

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Pfizer initially proposed the following indication in their NDA submission:

"IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease".

During the review process the indication was modified to the following:

"IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease."

6.1.1 Methods

The single trial supporting the efficacy review of this NDA is the randomized Phase 2 portion of PALOMA-1 (A5481003). For detailed information on PALOMA-1 trial design see Section 5.3.1. For the statistical review, please see Dr. Erik Bloomquist's review. As mentioned earlier, this efficacy analysis will not take into account the non-randomized Phase 1 portion of PALOMA-1. The Phase 2 portion of the study was a randomized, open-label multi-national trial with two Parts which were determined by biomarker status. The primary analysis population or ITT population was all randomized patients from the Phase 2 study (both Part 1 and Part 2 combined).

6.1.2 Protocol Deviations

Overall there was a large percentage of protocol deviations in study A5481003 as summarized in Table 11. Specifically protocol deviations occurred with respect to inclusion/exclusion criteria, randomization, deviations from the conduct of the study and study assessments. Investigational product deviations reflected that the exact study drug dose and schedule were not adhered to with typically just a few dosing errors. Many of the laboratory protocol deviations were related to lab testing not being done in a given cycle or PK deviations.

Notable deviations included multiple patients being stratified incorrectly at randomization. The stratification factors for these patients used for randomization were different than what was reported on the CRF (assumed to be the accurate variable). Please see Section 6.1.11 for an analysis of PFS based on the data in the CRF.
Within the visit schedule and procedure/tests were a few assessments of tumor status that were outside of the window allowed. These deviations typically were only two to three weeks outside of the window or had subsequent assessments without progression. According to the investigator assessment, only one patient had missed assessments immediately before progression and the patient was appropriately censored (SID 10553003). Other important deviations include patients being treated with bisphosphonates who were not receiving treatment upon entering the study. Bisphosphonate use is further detailed in Section 6.1.3.

Significant protocol deviations as determined by the applicant had only 1 or 2 patients in each category except for inclusion/exclusion. These inclusion/exclusion deviations included: failure to determine postmenopausal status (n=4), ALT/AST levels being elevated and failure to demonstrate a measurable lesion in that same patient (SID 10102001), failure to obtain a tissue sample prior to randomization (SID 10542002), radiation therapy given within 2 weeks of randomization (SID 10523005), a patient on tamoxifen who continued with palbociclib refusing to take letrozole (SID 11023003), and a patient who received prior anti-cancer therapy for advanced disease (SID 11053004).

Table 12: Protocol Deviation Table

Protocol Deviation Category	Total Phase 2 (N=165)	Palbo/Let Phase 2 Total (N=84) n (%)	Letrozole Phase 2 Total (N=81) n (%)	Palbo/Let Phase 2 Part 1 (N=34) n (%)	Letrozole Phase 2 Part 1 (N=32) n (%)	Palbo/Let Phase 2 Part 2 (N=50) n (%)	Letrozole Phase 2 Part 2 (N=49) n (%)
Any Protocol Deviation	154 (93.3)	83 (98.8)	71 (87.7)	33 (97.1)	28 (87.5)	50 (100%)	43 (87.8)
Inclusion/Exclusion	17 (10.3)	8 (9.5)	9 (11.1)	1 (2.9)	6 (18.8)	7 (14)	3 (6.1)
Investigational Product	62 (37.6)	48 (57.1)	14 (17.3)	17 (50)	4 (12.5)	31 (62)	10 (20.4)
Concomitant Medications	8 (4.8)	2 (2.4)	6 (7.4)	0	2 (6.3)	2 (4)	4(8.2)
Laboratory	105 (63.6)	59 (70.2)	46 (56.8)	22 (64.7)	19 (59.4)	37 (74)	27 (55.1)
Visit Schedule	71 (43)	39 (46.4)	32 (39.5)	11 (32.4)	10 (31.3)	28 (56)	22 (44.9)
Procedure/Tests	129 (78.2)	71 (84.5)	58 (71.6)	30 (88.2)	21 (65.6)	41 (82)	37 (75.5)
Randomization	33 (20)	18 (21.4)	15 (18.5)	8 (23.5)	8 (25)	10 (20)	7 (14.3)
Safety Reporting	9 (5.5)	7 (8.3)	2 (2.5)	4 (11.8)	0	3 (6)	2 (4.1)
Protocol-Specific Discontinuation Criteria	3 (1.8)	1 (1.2)	2 (2.5)	1 (2.9)	2 (6.3)	0	0
Other	24 (14.5)	14 (16.7)	10 (12.3)	7 (20.9)	2 (6.3)	7 (14)	8 (16.3)
Any Significant Protocol Deviation	14 (8.5)	8 (9.5)	6 (7.4)	1 (2.9)	3 (9.4)	7 (14)	3 (6.1)
Inclusion/Exclusion	12 (7.3)	6 (7.1)	6 (7.4)	1 (2.9)	3 (9.4)	5 (10)	3 (6.1)
Investigational Product	2 (1.2)	2 (2.4)	0	0	0	2 (4)	0
Procedure/Tests	2 (1.2)	0	2 (2.5)	0	1 (3.1)	0	1 (2)
Randomization	1 (0.6)	0	1 (1.2)	0	1 (3.1)	0	0

Palbo: palbociclib; Let: letrozole
Source: CSR Table 16.2.2

***Reviewer Comment**: The review team thoroughly reviewed the protocol deviations in both study arms and concluded that these deviations did not impact the overall efficacy results. Particularly the safety reporting, laboratory, investigational product deviations would not seem to have affected the study. With only one exception which was censored appropriately, missed assessments were not followed by progression events so likely did not affect efficacy and were well balanced between arms. While eight patients were treated with bisphosphonates after enrollment which could have helped stabilize bone disease, seven of these eight bisphosphonate deviations occurred on the letrozole alone arm thus not biasing the study toward palbociclib benefit (see Section 6.1.3 for more details).*

6.1.3 Demographics

Enrollment by Country:
Table 12 presents the breakdown of enrollment by county. The 4 highest accruing countries were The United States, Hungary, Germany and Ukraine.

Table 13: PALOMA-1 (Phase 2) Enrollment by country

Country n (%)	Palbociclib + Letrozole (n=84)	Letrozole (n=81)
United States	13 (15.5)	18 (22.2)
Hungary	12 (14.3)	14 (17.3)
Germany	14 (16.7)	11 (13.6)
Ukraine	10 (11.9)	14 (17.3)
Ireland	11 (13.1)	7 (8.6)
Spain	9 (10.7)	6 (7.4)
Russian Federation	7 (8.3)	3 (3.7)
Canada	1 (1.2)	4 (4.9)
Korea	2 (2.4)	3 (3.7)
Italy	2 (2.4)	1 (1.2)
France	2 (2.4)	0
South Africa	1 (1.2)	0

Source: CSR Table 14.1.2.6.1

***Reviewer Comment**: Diverse international representation, including 18.8% from The United States. When sensitivities analyses were performed by country there was no significant change to the overall efficacy results.*

Baseline Demographics:
Demographic information is represented in Table 13. Demographics are generally balanced across treatment arms and within the two Parts of the study.

Table 14: Baseline Demographics

	Phase 2 (Part 1 and Part 2)		Phase 2 Part 1		Phase Part 2	
	Palbociclib Letrozole (n=84)	Letrozole (n=81)	Palbociclib Letrozole (n=34)	Letrozole (n=32)	Palbociclib Letrozole (n=50)	Letrozole (n=49)
Age (years), n (%)						
18-44	2 (2.4)	4 (4.9)	2 (5.9)	2 (6.3)	0	2 (4.1)
45-64	45 (53.6)	38 (46.9)	15 (44.1)	15 (46.9)	30 (60.0)	23 (46.9)
≥ 65	37 (44)	39 (48.1)	17 (50.0)	15 (46.9)	61.7 (9.56)	63 (9.62)
Median (years)	62.5 (41 to 89)	64 (38 to 84)	65.5 (41 to 89)	64.0 (42 to 75)	62.0 (46 to 83)	63.0 (38 to 84)
Race, n (%)						
White	76 (90.5)	72 (88.9)	31 (91.2)	26 (81.3)	45 (90.0)	46 (93.9)
Black	1 (1.2)	1 (1.2)	1 (2.9)	1 (3.1)	0	0
Asian	6 (7.1)	4 (4.9)	2 (5.9)	1 (3.1)	4 (8.0)	3 (6.1)
Other	1 (1.2)	4 (4.9)	0	4 (12.5)	1 (2.0)	0
ECOG PS, n (%)						
0	46 (54.8)	45 (55.6)	23 (67.6)	20 (62.5)	23 (46.0)	25 (51.0)
1	38 (45.2)	36 (44.4)	11 (32.4)	12 (37.5)	27 (54.0)	24 (49.0)

Source: CSR Table18

***Reviewer Comment**: There is an underrepresented Black population considering the U.S. patient who is diagnosed with breast cancer. Unfortunately most clinical trials have similar underrepresentation. There were no men enrolled in the study and therefore it will be difficult to assess the treatment of men with palbociclib. The median age reflects that of the overall U.S. population diagnosed with breast cancer.*

Baseline Disease Characteristics:

Baseline disease characteristics are shown in Table 14. There is a difference between treatment arms with respect to median duration since diagnosis with a shorter time being seen on the palbociclib plus letrozole arm than on the letrozole alone arm (1.3 years vs. 2.4 years). Accounting for some of this difference is the increased percentage of de novo disease seen in the palbociclib plus letrozole arm vs. the letrozole alone arm (52.3% vs. 45.7%). In addition, the histologic grade showed an imbalance with more patients (36.9%) on the palbociclib plus letrozole arm having grade 3 tumor compared to the letrozole alone arm (22.2%). Measurable disease was well balanced between treatment arms. Between the two parts of the study there were also some differences. A higher percentage of patients had ductal carcinoma (82.4% vs. 70%) in the Part 1 and Part 2 cohorts respectively. Within the letrozole alone arm a lower percentage of patient had grade 3 tumors (9.4% vs. 30.6%) and a lower percentage of patients had measurable disease at baseline (71.9% vs. 87.8%) in the Part 1 and Part 2 cohorts.

Three patients had locally advanced disease (two on the palbociclib plus letrozole arm and one on the letrozole alone arm), and 163 had metastatic disease (98.2%).

Table 15: Baseline Disease Characteristics

	Phase 2 (Part 1 and Part 2)		Phase 2 Part 1		Phase 2 Part 2	
	Palbociclib Letrozole (n=84)	Letrozole (n=81)	Palbociclib Letrozole (n=34)	Letrozole (n=32)	Palbociclib Letrozole (n=50)	Letrozole (n=49)
Duration Since Diagnosis of Breast Cancer (years)						
Median	1.3 (0 to 27)	2.4 (0 to 40)	0.9 (0 to 27)	3.4 (0 to 33.9)	1.5 (0 to 25)	2.1 (0 to 40)
Mean	4.5	6.1	5.1	7.2	4.2	5.5
De Novo Disease, n (%)						
Yes	44(52.3)	37 (45.7)	19 (55.9)	17 (53.1)	25 (50)	20 (40.8)
No	40(47.6)	44 (54.3)	15 (44.1)	15 (46.9)	25 (50)	29 (59.2)
Histopathologic Classification, n (%)						
Ductal	63 (75)	54 (66.7)	28 (82.4)	21 (65.5)	35 (70.0)	33 (67.3)
Lobular	18 (21.4)	19 (23.5)	5 (14.7)	9 (28.1)	13 (26.0)	10 (20.4)
Other	3 (3.6)	8 (9.9)	1 (2.9)	2 (6.3)	2 (4)	6 (12.2)
Histologic Grade, n (%)						
1	8 (9.5)	10 (12.3)	6 (17.6)	7 (21.9)	2 (4.0)	3 (6.1)
2	31 (36.9)	38 (46.9)	9 (26.5)	16 (50.0)	22 (44.0)	22 (44.9)
3	31 (36.9)	18 (22.2)	14 (41.2)	3 (9.4)	17 (34.0)	15 (30.6)
Progesterone Receptor, n (%)						
Positive	65 (77.4)	53 (65.4)	23 (67.6)	18 (56.3)	42 (84.0)	35 (71.4)
Negative	11 (13.1)	23 (28.4)	5 (14.7)	10 (31.3)	6 (12.0)	13 (26.5)
Measurable Disease, n (%)						
Yes	65 (77.4)	66 (81.5)	27 (79.4)	23 (71.9)	38 (76)	43 (87.8)
No	19 (22.6)	15 (18.5)	7 (20.6)	9 (28.1)	12 (24.0)	6 (12.2)

Source: CSR Table 19

Pre- and Post-Study Systemic Therapy for Breast Cancer:

Prior treatments for cancer under study were generally well balanced between the treatment arms (Table 15). However, a lower percentage of patients in the palbociclib plus letrozole arm received just one prior regimen (29.8%) compared with the letrozole alone arm (39.5%) indicating that more patients on the palbociclib plus letrozole arm had received more than one prior regimen (17.1%).

A lower percentage of patients in the palbociclib plus letrozole arm (57.1%) received follow-up systemic therapy compared with the letrozole alone arm (76.5%) likely due to the fact that at data cut off more patients were still on study in the palbociclib plus letrozole arm (22.6% compared to 9.9%) and thus were counted as not receiving follow-

up therapy. In the Palbociclib plus letrozole arm, 36.9% of patients received one regimen and 20.2% received two or more lines of therapy. In the letrozole alone arm, 45.7% of patients received one additional regimen and 30.8% received two or more regimens.

Table 16: Prior Breast Cancer Treatment

	Phase 2 (Part 1 and Part 2)		**Phase 2 Part 1**		**Phase 2 Part 2**	
	Palbociclib Letrozole (n=84)	**Letrozole (n=81)**	**Palbociclib Letrozole (n=34)**	**Letrozole (n=32)**	**Palbociclib Letrozole (n=50)**	**Letrozole (n=49)**
Prior Systemic Therapy, n (%)						
No	44 (52.3)	37 (45.7)	19 (55.9)	17 (53.1)	25 (50)	20 (40.8)
Prior Anthra-cycline	26 (31.0)	25 (30.9)	10 (29.4)	12 (37.5)	16 (32.0)	13 (26.5)
Prior Taxane	12 (14.3)	14 (17.3)	6 (17.6)	7 (21.9)	6 (12.0)	7 (14.3)
Prior Hormonal	27 (32.1)	28 (34.6)	11 (32.4)	11 (34.4)	16 (32.0)	17 (34.7)
Prior Radiation, n (%)						
Prior Radiation	46 (54.8)	38 (46.9)	19 (55.9)	15 (46.9)	27 (54.0)	23 (46.9)
Prior Surgery, n (%)						
Prior Surgery	68 (81)	66 (81.5)	32 (94.1)	30 (93.8)	36 (72)	36 (73.5)

Source: CSR Table21and 22

Reviewer Comment*: The patient population studied in PALOMA-1 had a few important differences when considering a U.S. patient population. Lobular cancers were overrepresented in the study; in the U.S. approximately 10-15% of patients are diagnosed with lobular breast cancer. This small difference is unlikely to impact the interpretation of the study results. A larger issue is the diagnosis of de novo disease. In the U.S. only 5% of patients are diagnosed with de novo disease and in the randomized Phase 2 PALOMA-1 study 49.1% of subjects had de novo disease. The U.S. population on the study was comprised of 35.5% de novo disease reflecting the small sample size. The high level of de novo disease indicates that patients enrolled in this trial may represent a more aggressive disease phenotype than the typical US population. Given that the distribution of de novo disease was seen in a greater percentage of patients on the palbociclib plus letrozole arm it is unlikely to have biased the results and if anything would have been indicative of more aggressive disease that might demonstrate a more rapid progression. This could be a reason why the control arm appears to be performing slightly less well than historical controls (see Section 6.1.5 for more details).*

Stratification Factors:

Patients were stratified based on site of disease (visceral vs. bone only vs. other) and based on disease free interval (> 12 months from prior diagnosis vs. <12 months or de novo disease). Incorrect stratification factors were used at the time of randomization for many patients. Thus while in the ITT population the stratification factors are balanced across the treatment arms, when using the case report form (CRF) data there are imbalances between the treatment arms. A lower percentage of patients had visceral disease in the palbociclib plus letrozole arm (44.1%) compared to the letrozole alone arm (53.1%) and a higher percentage of patients had bone only disease in the palbociclib plus letrozole arm (20.2%) compared to the letrozole alone arm (14.8%). Within Part 1 of the study a lower percentage of patients had visceral disease in both arms compared to both arms of the Part 2 study. These imbalances are shown in Table 16.

Table 17: Stratification Factors

	Phase 2 (Part 1 and Part 2)		Phase 2 Part 1		Phase 2 Part 2	
	Palbociclib Letrozole (n=84)	Letrozole (n=81)	Palbociclib Letrozole (n-34)	Letrozole (n=32)	Palbociclib Letrozole (n=50)	Letrozole (n=49)
Disease Site (based on randomization)						
Visceral	39 (46.4)	40 (49.4)	12 (35.3)	11 (34.4)	27 (54.0)	29 (59.2)
Bone only	17 (20.2)	14 (17.3)	8 (23.5)	7 (21.9)	9 (18.0)	7 (14.3)
Other	28 (33.3)	27 (33.3)	14 (41.2)	14 (43.8)	14 (28.0)	13 (26.5)
Disease Site (based on CRF)						
Visceral	37 (44.1)	43 (53.1)	10 (29.4)	11 (34.4)	25 (54.0)	32 (65.3)
Bone only	17 (20.2)	12 (14.8)	7 (20.6)	6 (18.8)	10 (20.0)	6 (12.2)
Other	30 (35.7)	26 (32.1)	17 (50.0)	15 (46.5)	13 (26.0)	11 (22.5)
Disease Free Interval (based on randomization)						
>12 months	37 (44.1)	36 (44.4)	14 (41.2)	13 (40.6)	23 (46.0)	23 (46.9)
<12 months or de novo	47 (56.0)	45 (55.6)	20 (58.8)	19 (59.4)	27 (54.0)	26 (53.1)
Disease Free Interval (based on CRF)						
>12 months	25 (29.8)	30 (37.0)	10 (29.4)	10 (31.3)	15 (30.0)	10 (40.8)
<12 months or de novo	59 (70.2)	51 (63.0)	24 (70.6)	22 (68.8)	35 (70.0)	29 (59.2)

Source: CSR Table 20

***Reviewer Comment**: Although patients were stratified incorrectly we performed sensitivity analyses of PFS using CRF data and the PFS analysis remained in favor of the palbociclib plus letrozole arm (described in Section 6.1.11).*

Concomitant Medication and Therapy:

In both arms of the study a similar number of patients received concomitant medications (78 patients (94%) and 74 patients (96.1%) in the palbociclib plus letrozole arm and letrozole alone arm respectively). Bisphosphonates were a common concomitant medication and bisphosphonate use is summarized in Table 17. In general the bisphosphonate use on study was similar between treatment arms. There were eight patients who were newly initiated on bisphosphonates during treatment. There were

also four patients who underwent surgery while on treatment, three of the four were censored at the time of surgery for receiving anti-cancer treatment prior to progression. The fourth (SID: 10193004) was censored by the BICR eight months prior to a progression event by the investigator as this patient's lesion (breast) undergoing surgery was not deemed a target lesion by the investigator. This patient was on the letrozole only arm. Radiation was allowed per protocol for palliation of symptoms to lesions that were not progressive. Eleven patients had radiation to bone lesions on study and two (on the letrozole arm) of these patients had radiation to the only site of their disease. None of these eleven patients were censored for radiation therapy as all met criteria listed in the protocol for palliative treatment of non-progressive lesions.

Table 18: Concomitant Bisphosphonates on Study

	Palbo/Let Phase 2 N=83	Letrozole Phase 2 N=77	Palbo/Let Part 1 N=33	Letrozole Part 1 N=29	Palbo/Let Part 2 N=50	Letrozole Part 2 N=48
Alendronate sodium	0	2	0	1	0	1
Alendronic acid	1	0	1	0	0	0
Clodronate	0	2	0	1	0	1
Clodronic acid	0	1	0	1	0	0
Denosumab	3	7	0	2	3	5
Ibandronic acid	4	6	0	2	4	1
Ibandronate sodium	2	0	2	0	0	0
Pamidronic acid	0	5	0	0	0	5
Pamidronate	5	5	4	2	1	3
Raloxifene	1	0	1	0	0	0
Zoledronic Acid	28	34	15	16	13	18
Total	45 (54%)	62 (80%)	23 (70%)	25 (86%)	21 (42%)	34 (70%)

Palbo: palbociclib; Let: letrozole
Source: Modified from Applicant Table 14.4.2.4.b

Reviewer Comment:
The eight patients who were newly initiated on bisphosphonates during treatment could have had stabilization of their bone metastasis thus confounding the results. However, seven of these eight patients were on the letrozole alone arm, thus it is not thought that these deviations would have affected the study in favor of palbociclib effect. The surgeries were either treated appropriately with censoring or in the one case where the patient was not censored by the investigator the patient remained on the letrozole arm for an additional eight months prior to progressing. Similarly the patients treated with

radiation to their only site of disease were both on the letrozole arm. All of these instances might only have benefited the letrozole arm and thus do not call into question the interpretation of the results.

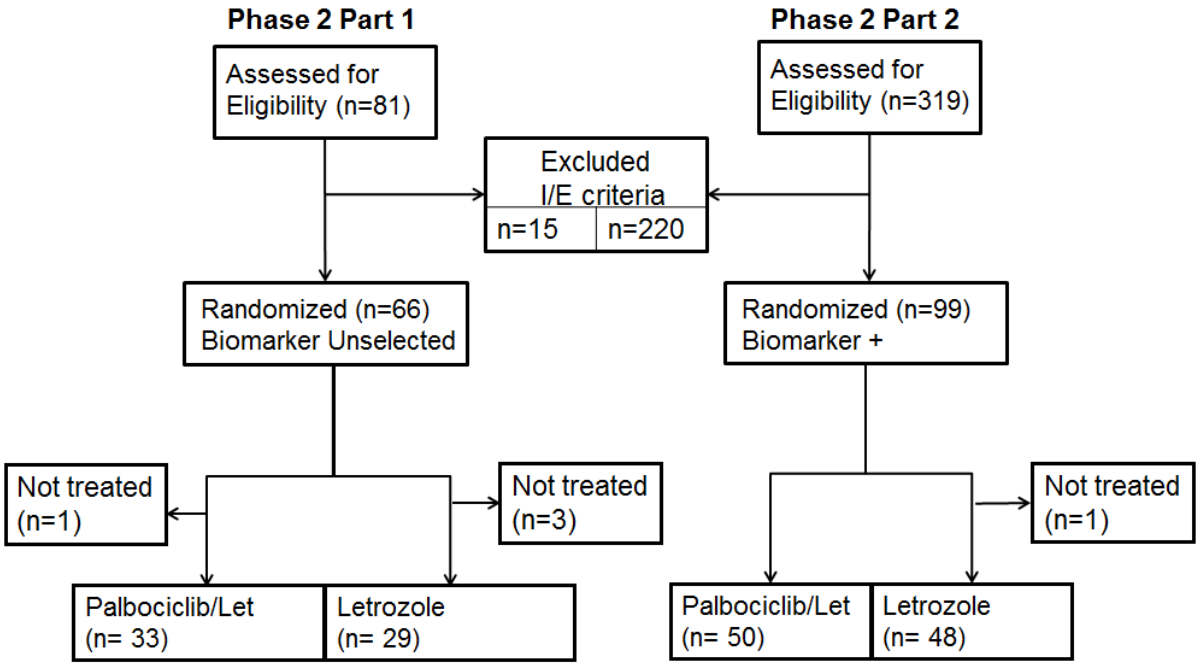
6.1.4 Subject Disposition

From December 22nd, 2009 to May 12th, 2012, a total of 165 women were randomized. These 165 women represent the number available for the primary efficacy analysis (ITT). The total number of patients screened was 400. Since Part 2 was only a biomarker positive population this accounted for the larger number of the screen failures. See Figure 4 for a consort diagram of patient enrollment and randomization.

In the Phase 2 study, 84 patients were randomized to the palbociclib plus letrozole arm and 81 patients were randomized to the letrozole alone arm and thus make up the ITT analysis population. Five patients were randomized but not treated, one in the palbociclib plus letrozole arm and four in the letrozole alone arm. The Part 1 portion included 34 and 32 patients respectively on the palbociclib plus letrozole and letrozole alone arm and the Part 2 portion included 50 and 49 patients respectively on the palbociclib plus letrozole and letrozole alone arm.

At the time of the data cut off on November 29th, 2013, 26 patients were still ongoing in the study with 19 (22.6%) on the palbociclib plus letrozole arm and 8 (9.9%) on the letrozole alone arm. One patient in the palbociclib plus letrozole arm died at end of treatment. At the end of study, 30 (35.7%) patients on the palbociclib plus letrozole arm had died and 31 (38.3%) on the letrozole alone arm had died. Forty nine (58.3%) patients on the palbociclib plus letrozole arm and 42 (51.9%) on the letrozole alone arm were alive and being followed.

Figure 4: Patient Enrollment and Randomization in Trial A5481003



I/E: Inclusion/Exclusion criteria (165 for not meeting biomarker criteria in Part 2)
Source: CSR Table 14.1.1.1.b

6.1.5 Analysis of Primary Endpoint(s)

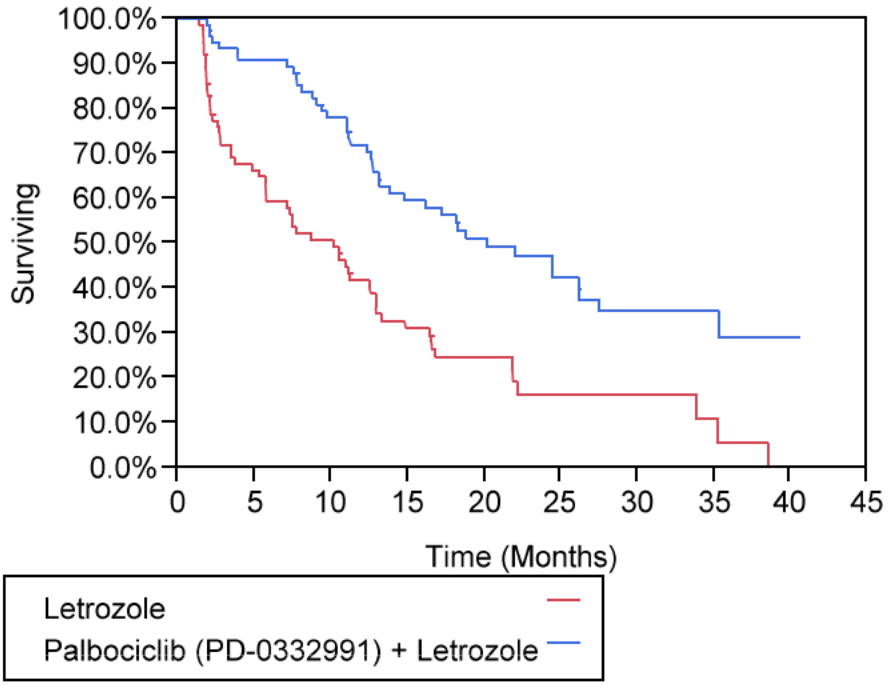
The primary endpoint of the Phase 2 study was investigator-assessed PFS in the combined (Part 1 and Part 2) population. As of the November 2013 data cut-off, 100 investigator-assessed PFS events had occurred, 41 (48.8%) in the palbociclib plus letrozole arm and 59 (72.8%) in the letrozole alone arm. The median PFS in the palbociclib plus letrozole arm was 20.2 months compared to 10.2 months in the letrozole alone arm, (HR=0.488, 95% CI: 0.319-0.748; p=0.0004), as summarized in Table 18 and Figure 5.

Table 19: Primary endpoint: Investigator-assessed PFS

	Palbociclib + Letrozole N=84	Letrozole N=81
Number of events (%)	41 (48.8%)	59 (72.8%)
Censored (%)	43 (51.2%)	22 (27.2%)
Median PFS (months) **95% CI**	20.2 (13.8-27.5)	10.2 (5.7-12.6)
Hazard Ratio (stratified)* **95% CI** **p-value#**	0.488 (0.319 to 0.748) 0.0004	

*Stratified by disease-free interval and disease site
#1-sided p-value from the log-rank test stratified by stratification factors per randomization and Part
Source: eedrsp.xpt

Figure 5: KM Curve Investigator Assessed PFS



Source: eedrsp.xpt

Reviewer Comment: *A clinically meaningful and statistically significant 10 month improvement in median PFS was seen.*

Analysis was also performed on investigator-assessed PFS by Part of the study and is shown in Table 19 and Figure 6. In Part 1, the biomarker unselected population, the palbociclib plus letrozole arm demonstrated a median improvement in PFS of 20.4 months (HR=0.299, 95% CI: 0.156-0.572; p<0.0001), and in Part 2, the biomarker

selected patient population, the palbociclib plus letrozole arm showed a median improvement in PFS of 7 months (HR=0.508, 95% CI: 0.303-0.853; p=0.0046).

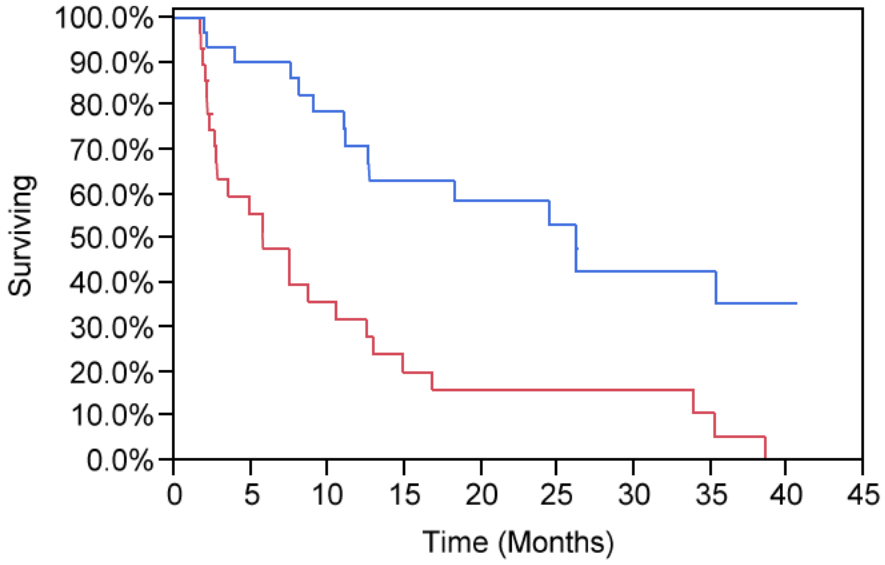
Table 20: Investigator-assessed PFS by Part

	Part 1 N=66		Part 2 N=99	
	Palbo/Let N=34	**Letrozole N=32**	**Palbo/Let N=50**	**Letrozole N=49**
Number of events (%)	15 (44.1)	25 (78.1)	26 (52)	34 (69.4)
Censored (%)	19 (55.9)	7 (21.9)	24 (48)	15 (30.6)
Median PFS 95% CI	26.1 months (11.2-NR)	5.7 months (2.6-10.5)	18.1 months (13.1-27.5)	11.1 months (7.1-16.4)
Hazard Ratio 95% CI p- value*	0.299 (0.156-0.572) <0.0001		0.508 (0.303-0.853) 0.0046	

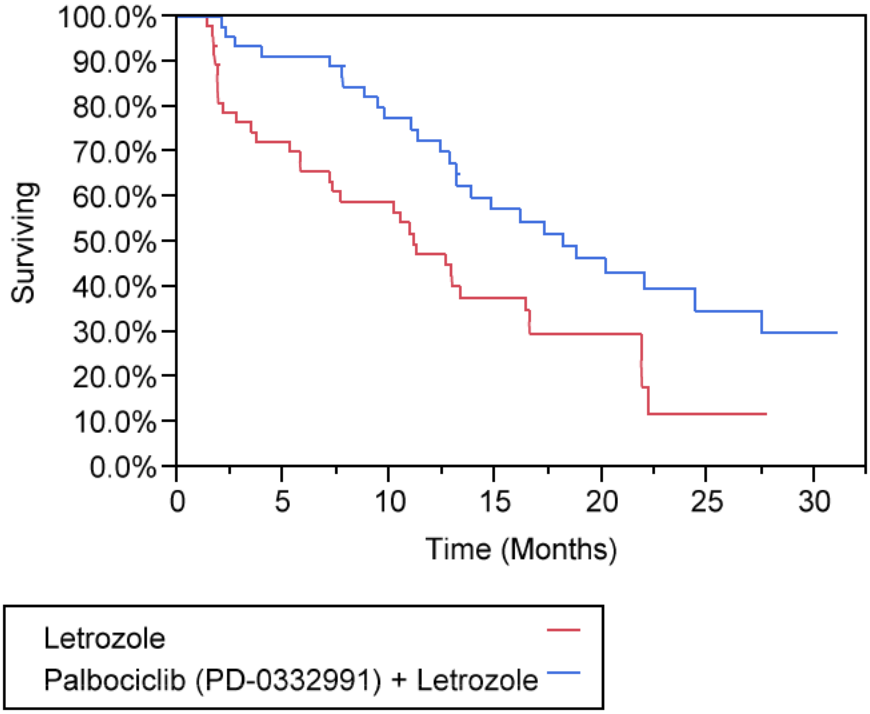
Palbo: Palbociclib; Let: Letrozole; NR: not reached
*1-sided p-value from the log-rank test
Source: eedrsp.xpt

Figure 6: KM Curve Investigator-assessed PFS by Part

A. Part 1



B. Part 2



Source: eedrsp.xpt

Reviewer Comment: *An improvement in median PFS remains when the study is separated by Part, however the magnitude of benefit differs between Part 1 and Part 2. In Part 1 the control arm appears to have under-performed based on historical information with recent aromatase trials in the first-line advanced breast cancer setting demonstrating a 10.2 to 13.5 month PFS[25-27]. These studies used anastrozole as the control arm in the first-line advanced breast cancer setting. Aggressive baseline disease characteristics such as de novo disease in PALOMA-1 trial may explain the lower PFS seen in the letrozole alone arm. It is also possible that the biomarker positive population (amplification in CCND1 and/or CDKN2A loss) resulted in a smaller benefit of palbociclib plus letrozole compared to the biomarker unselected population. A further discussion on biomarker can be found in Sections 6.1.6 and 6.1.8. Another possibility reflecting the difference in Part 1 and Part 2 could be that the results were affected by a level of investigator bias. This possibility is further explored in the following sections.*

Sensitivity Analyses:
Seven planned sensitivity analyses were performed; results are listed in Table 20 for the analyses performed on the ITT population (combined Part 1 and Part 2).
Briefly, the sensitivity analyses performed were as follows:

- Sensitivity analysis 1: Analysis using the same methods as the primary analysis except a 1-sided unstratified log-rank test was used to compare treatments and the HR was based on an unstratified Cox proportional hazards model.
- Sensitivity analysis 2: Stratified analysis per the stratification factors reported on the Case Report Form.

- Sensitivity analysis 3: Incorporating symptomatic deterioration as an event and stratified by Part.
- Sensitivity analysis 4: Including disease progression or death occurring after 28 days of treatment discontinuation as an event (regardless of initiation of additional anticancer therapy) and stratified by Part.
- Sensitivity analysis 5: PFS analyzed by forcing the actual assessment times to the planned times (every 8 weeks) and stratified by Part.
- Sensitivity analysis 6: PFS analyzed for the All Treated as Treated Population and stratified by Part.
- Sensitivity analysis 7: Multivariate analysis of PFS of treatment effect controlling for individual baseline factors and stratified by Part.

Table 21: PFS Sensitivity analyses in ITT population (Reviewer Table)

PFS analyses	Median (months)		HR (95% CI)	P-value	Palbo/Let events	Let events
	Palbo/Let	Letrozole				
INV PFS	20.2	10.2	0.488 (0.319-0.748)	0.0004	41	59
Sensitivity Analysis 1	20.2	10.2	0.412 (0.275-0.617)	<0.0001	41	59
Sensitivity Analysis 2	20.2	10.2	0.459 (0.301-0.700)	0.0001	41	59
Sensitivity Analysis 3	18.6	7.7	0.442 (0.300-0.652)	<0.0001	46	62
Sensitivity Analysis 4	18.8	10.2	0.452 (0.304-0.617)	<0.0001	44	59
Sensitivity Analysis 5	20.3	9.2	0.416 (0.277-0.624)	<0.0001	41	59
Sensitivity Analysis 6	20.2	10.2	0.411 (0.274-0.616)	<0.0001	41	59
Sensitivity Analysis 7	NC	NC	0.416 (0.276-0.628)	<0.0001	41	59

Palbo: palbociclib; Let: letrozole; CI: Confidence interval; HR: Hazard ratio; NC: Not calculated; P-value: 1-sided p-value.
Source: eedrsp.xpt, ptevnt.xpt

Reviewer Comment*: Planned sensitivity analyses are consistent with the primary efficacy endpoint.*

6.1.6 Analysis of Secondary Endpoints(s)

PFS Based on Blinded Independent Central Review (BICR):

The applicant retrospectively collected and submitted radiographic images to a third party for BICR by (b) (4). Of the 165 patients images for 161 were

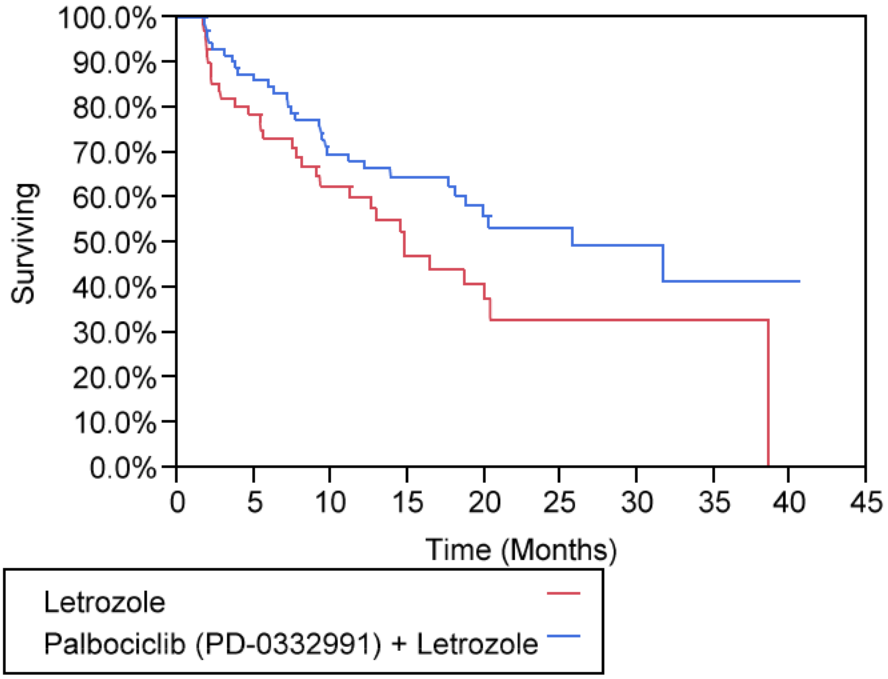
read by the BICR. The four missing patients were equally distributed from each arm of the study. In the combined population (Part 1 and Part 2) the BICR identified 64 PFS events (31 in the palbociclib plus letrozole arm and 33 in the letrozole alone arm). As shown in Table 21 and Figure 7, the median PFS in the palbociclib plus letrozole arm was 25.7 months (95% CI: 17.7, NR) and in the letrozole alone arm was 14.8 months (95% CI: 9.3, 20.4) with a HR of 0.621 (95% CI: 0.378, 1.019).

Table 22: BICR-assessed PFS

	Palbociclib + Letrozole N=84	**Letrozole N=81**
Number of events (%)	31 (36.9%)	33 (40.7%)
Censored (%)	53 (63.1%)	48 (59.3%)
Median PFS (months) **95% CI**	25.7 (17.7-NR)	14.8 (9.3-20.4)
Hazard Ratio (stratified)* **95% CI** **p-value#**	0.621 (0.378-1.019) 0.0286	

*Stratified by Part, #1-sided p-value from the log-rank test stratified by Part
Source: ptevnt.xpt

Figure 7: KM Curve BICR-assessed PFS



Source: ptevnt.xpt

***Reviewer Comment**: The BICR analysis was conducted at the request of the FDA. Note that the p-value is reported as one-sided. However, the 10 month improvement in*

median PFS is supportive of the investigator-assessed PFS. A further examination of the discordance between events in the BICR and investigator-assessed events will be further discussed below.

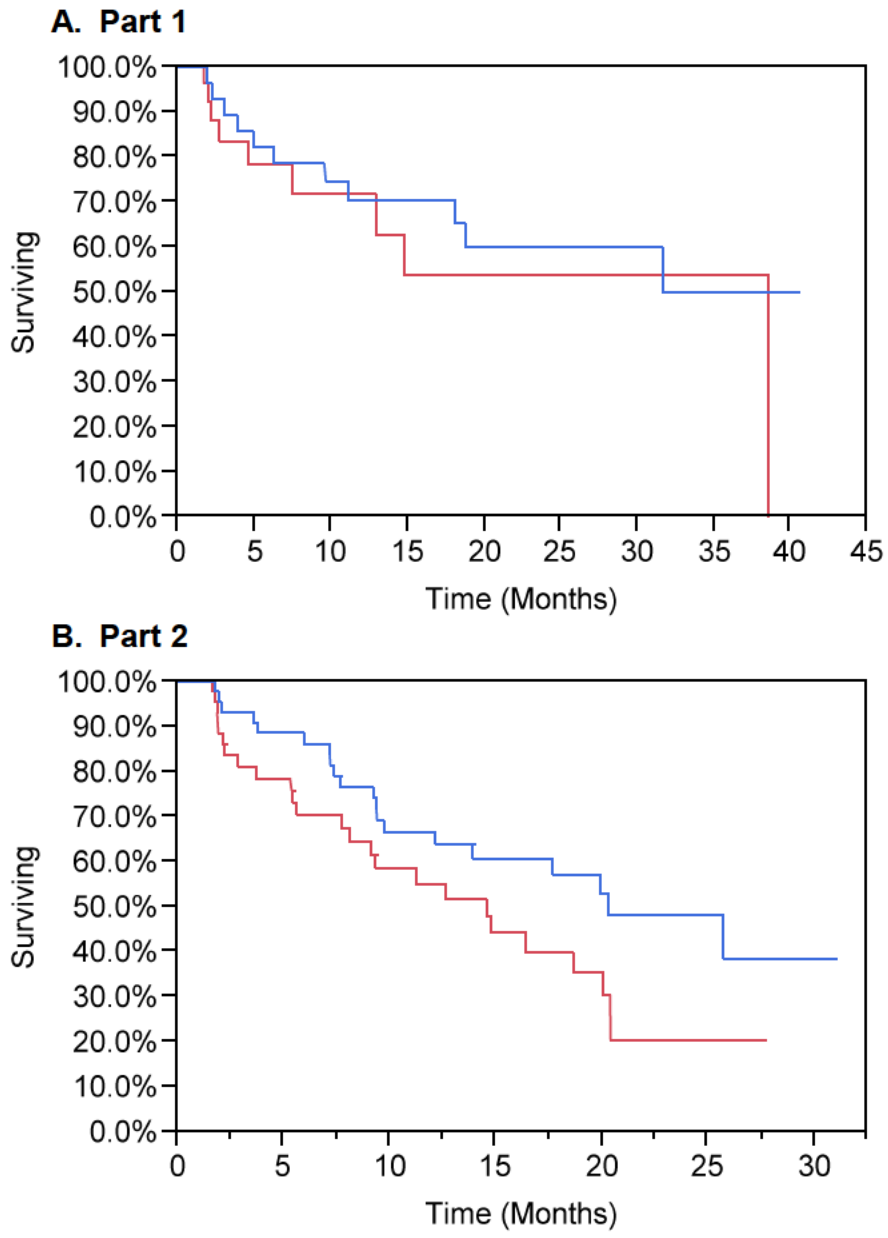
When Part 1 of the study was analyzed separately by BICR-assessment, the palbociclib plus letrozole arm failed to show statistical improvement over the letrozole arm with a HR of 0.731 (95% CI: 0.300, 1.779; p=0.2442). In Part 2 of the study the BICR-assessed findings demonstrated approximately a 6 month increase in median PFS with a HR of 0.576 (95% CI: 0.316, 1.050; p=0.0342). These results are depicted in Table 22 and Figure 8.

Table 23: BICR-assessed PFS by Part

	Part 1 N=66		**Part 2 N=99**	
	Palbo/Let N=34	**Letrozole N=32**	**Palbo/Let N=50**	**Letrozole N=49**
Number of events (%)	11 (32.4%)	9 (28.1%)	20 (40%)	24 (49%)
Censored (%)	23 (67.6%)	23 (71.9%)	30 (60%)	25 (51%)
Median PFS 95% CI	31.6 (11.2-NR)	38.6 (7.5-38.6)	20.3 (12.2-NR)	14.6 (8.1-20.0)
Hazard Ratio 95% CI p- value*	0.731 (0.300-1.779) 0.2442		0.576 (0.316-1.050) 0.0342	

Palbo: palbociclib; Let: letrozole; NR: not reached
*1-sided p-value from the log-rank test
Source: ptevnt.xpt

Figure 8: KM Curve BICR-assessed PFS by Part



Source: ptevnt.xpt

Additionally all seven prospectively defined sensitivity analyses were performed based on the BICR results and results are shown in Table 23. These sensitivity analyses based on BICR results show HRs ranging from 0.593 to 0.697.

Table 24: Sensitivity analyses based on BICR-assessed PFS

PFS analyses	Median (months)		HR (95% CI)	P-value	Palbo/ Let events	Let events
BICR PFS	25.7	14.8	0.621 (0.378, 1.019)	0.0286	31	33
Sensitivity Analysis 1	25.7	14.8	0.615 (0.376, 1.008)	0.0260	31	33
Sensitivity Analysis 2	25.7	14.8	0.697 (0.419, 0.159)	0.0810	31	33
Sensitivity Analysis 3	25.7	14.6	0.631 (0.393, 1.014)	0.0275	34	36
Sensitivity Analysis 4	25.7	14.6	0.593 (0.368, 0.954)	0.0148	32	37
Sensitivity Analysis 5	25.8	14.8	0.632 (0.385, 1.037)	0.0338	31	33
Sensitivity Analysis 6	25.7	14.8	0.621 (0.378, 1.019)	0.0286	31	33
Sensitivity Analysis 7	NC	NC	0.617 (0.353, 1.077)	0.0895	24	30

Palbo: palbociclib; Let: letrozole; CI: Confidence interval; HR: Hazard ratio; NC: Not calculated
P-value: 1-sided p-value.
Source: eedrsp.xpt, ptevnt.xpt

At the request of the FDA, the applicant conducted multiple ad hoc sensitivity analyses to explore the discrepancies between investigator and BICR-assessed events (shown in Table 24). Only one analysis based on BICR assessment which considered censored adverse events (AE) as disease progression did not show a statistically significant finding of prolonged median PFS in the palbociclib plus letrozole arm. Hazard ratios in the nine other analyses ranged from 0.476 to 0.608, 1-sided p-values <0.0001 to 0.0286. Sensitivity analysis 10 which was based on BICR assessment but considered all patients who were censored for anticancer treatment, AE, global deterioration, consent withdrawn, other reasons, and objective progression or relapse by the investigator as disease progression, the HR remained consistent at 0.537 (ranging from 0.378-0.763).

Table 25: Ad-hoc Sensitivity Analyses for Progression-Free Survival (Applicant Table)

Analysis	Number of Patients (P+L vs. L)	Number of Events (P+L vs. L)	Hazard Ratio (95% CI)	1-sided p-value
Investigator assessment (primary analysis)	**84 vs. 81**	**41 vs. 59**	**0.488 (0.319-0.748)**	**0.0004**
BICR (secondary analysis)	**84 vs. 81**	**31 vs. 33**	**0.621 (0.378-1.019)**	**0.0286**
SA 1. Combined INV and BICR data (event) together. If both called PD, BICR data was used as the event time. BICR censoring data was used for censoring observations.	84 vs. 81	50 vs. 60	0.519 (0.355-0.760)	0.0003
SA 2. Combined INV and BICR data (event) together. If both called PD, the shortest time between them was used as the event time. INV censoring data was used for censoring observations.	84 vs. 81	50 vs. 60	0.540 (0.369-0.789)	0.0006
SA 3. Combined INV and BICR data (event) together. If both called PD, the shortest time between them was used as the event time in the P+L arm and the longest time between them was used as the event time in the L arm. INV censoring data was used for censoring observations.	84 vs. 81	50 vs. 60	0.557 (0.381-0.814)	0.0011
SA 4. Based on BICR data. If both BICR and INV called PD, replaced BICR time with INV time as the event time.	84 vs. 81	31 vs. 33	0. 578 (0.352-0.951)	0.0144
SA 5. Based on INV data. Censoring for AE was considered as PD.	84 vs. 81	49 vs. 60	0.476 (0.324-0.698)	<0.0001
SA 6. Based on BICR data. Censoring for AE was considered as PD.	84 vs. 81	37 vs. 34	0.703 (0.439-1.126)	0.0704
SA 7. Based on INV data. Censoring for anticancer treatment, AE, global deterioration, withdrew consent, and other reasons were considered as PD.	84 vs. 81	58 vs. 69	0.498 (0.349-0.711)	<0.0001
SA 8. Based on BICR data. Censoring for anticancer treatment, AE, global deterioration, withdrew consent, and other reasons were considered as PD.	84 vs. 81	44 vs. 47	0.608 (0.401-0.921)	0.0089
SA 9. Based on BICR data. Censoring for objective progression or relapse by INV was considered as PD.	84 vs. 81	46 vs. 56	0.526 (0.354-0.782)	0.0006
SA 10. Based on BICR data. Censoring for anticancer treatment, AE, global deterioration, withdrew consent, other reasons, and objective progression or relapse by INV were considered as PD.	84 vs. 81	59 vs. 70	0.537 (0.378-0.763)	0.0002

P=palbiciclib; L=Letrozole; SA: sensitivity analysis; CI=confidence interval; BICR=Blinded Independent Central Review; INV=investigator; PD=disease progression; AE=adverse event
Source: 14.2.13.3.b

***Reviewer Comment**: Planned sensitivity analyses showed a consistent benefit of the palbociclib plus letrozole arm with median PFS improvement of eight to ten months in all analyses by investigator or BICR assessment. Ad hoc sensitivity analyses also corroborated the overall findings with HRs ranging from 0.476 to 0.703. The demonstration of maintained effectiveness in these multiple analyses strengthens the robustness of the data.*

BICR Censoring:

There was an imbalance in censoring rates between the two treatment arms within the BICR assessment with the primary reason for censoring due to the patient discontinuing treatment (usually for progressive disease as assessed by the investigator) prior to BICR assessment of progression (see Table 25). This difference was particularly apparent in Part 1 of the study where 4 patients in the palbociclib plus letrozole arm (accounting for 17.4% of the censored patients) compared to 13 patients in the letrozole alone arm (accounting for 56.5% of the censored patients) were censored for BICR assessment of stable disease and progressive disease by the investigator.

Table 26: BICR Censoring

	Palbo/Let Phase 2	**Letrozole Phase 2**
Total Censored, n (%)	53 (63.1)	48 (59.3)
At Data-cut off, n (% of censored)	14 (32.6)	4 (8.3)
Off treatment prior to progression (as assessed by BICR), n (% of censored)		
- PD by INV	15 (34.8)	23 (47.9)
- Adverse Event	9 (20.9) neutropenia (4), PE, spinal pain, fatigue, asthenia, ischemic colitis	1 (2.1) arthralgia
- Clinical Progression	3 (7.0)	2 (4.2)
- Withdrew Consent	4 (9.3)	9 (18.8)
- Other	0	1 (2.1)
No Scans/data, n (% of censored)	2 (4.7)	2 (4.2)
No disease at baseline, n (% of censored)	1 (2.3)	1 (1.2)
Did not meet eligibility after randomization, n (% of censored)	1 (4.3)	1 (4.3)
Given new anti-cancer treatment, n (% of censored)	2 (4.7)	4 (8.3)
Unacceptable gap b/t disease progression and prior assessment, n (% of censored)	2 (4.7)	0

Palbo: palbociclib; Let: letrozole; PD: Progressive Disease
Source: Response to FDA Query 2/28/2014, Table 5 and Case report forms

For comparison, Table 26 shows the reasons for investigator censoring in PALOMA-2. The primary reason for censoring was due to patients in the palbociclib plus letrozole arm remaining on therapy at the study cut-off without investigator-assessed progression.

Table 27: Investigator Censoring

	Palbo/Let Phase 2	**Letrozole Phase 2**
Total Censored, n (%)	43 (51.2)	22 (27.2)
At data cut-off, n (% of censored)	19 (44.2)	6 (27.3)
Off treatment prior to progression, n (% of censored)		
- Adverse Event	11 (25.6) neutropenia (5), fallopian tube cancer, PE, spinal pain, fatigue, asthenia, ischemic colitis	2 (9.1) arthralgia and nausea
- Clinical Progression	5 (11.6)	3 (13.6)
- Withdrew Consent	5 (11.6)	7 (31.8)
- Other (MD said too many assessments for letrozole alone)		1 (4.5)
Did not meet eligibility after randomization, n (% of censored)	1 (2.3)	1 (4.5)
Given new anti-cancer treatment (surgery), n (% of censored)	1 (2.3)	2 (9.1)
Unacceptable gap b/t disease progression and prior assessment, n (% of censored)	1 (2.3)	

PD: Progressive Disease; Palbo: Palbociclib; Let: Letrozole.
Source: Response to FDA Query 2/28/2014, Table 4 and Case report forms

Table 27 shows the difference between certain categories of BICR and investigator assessment disagreements demonstrating that the investigator-assessed progressive disease with BICR-assessed stable disease by imaging was the primary driver of these discordances. Progression in the bone drove the majority of these discordances and was particularly pronounced in Part 1 of the study with 10 cases in the letrozole alone arm and only two cases in the palbociclib plus letrozole arm.

Table 28: Disagreements between BICR and Investigator Assessments

	Palbo/Let N=48 Phase 2	Letrozole N=48 Phase 2	Palbo/Let N=17 Part 1	Letrozole N=21 Part 1	Palbo/Let N=31 Part 2	Letrozole N=27 Part 2
INV PD BICR SD (by imaging)	16 (33.3%)	25 (52.1%)	5 (29.4%)	16 (76.2%)	11 (35.5%)	9 (33.3%)
• **INV PD in Bone**	6 (12.5%)	14 (29.2%)	2 (11.8%)	10 (47.6%)	4 (12.9%)	4 (14.8%)
INV SD BICR PD	9 (18.8%)	1 (2.1%)	3 (17.6%)	0 (0%)	6 (19.4%)	1 (3.7%)
INV PD BICR earlier PD	12 (25%)	14 (29.2%)	5 (29.4%)	2 (9.5%)	7 (22.6%)	12 (44.4%)

PD: Progressive Disease; SD: Stable Disease; INV: Investigator; Palbo: Palbociclib; Let: Letrozole
Source: CSR, Case Report Forms, Narratives

Reviewer Comment: *The inconsistent BICR-assessed PFS results in Part 1 of the study are likely due to a high amount of BICR censoring (low number of events) which accounted for the wide CI spread from 7.5 to 38.6 months in the letrozole alone arm and 11.2 months to not reached in the palbociclib plus letrozole arm. As described above, this high censoring was due to the investigator assessing progressive disease and taking the patient off treatment when BICR did not agree with the assessment. As shown above in Part 1 of the study this difference appears to have been driven by bone progression. Further sensitivity analyses looking at bone progression are described in Section 6.1.11 and are reassuring. It is known that bone lesion progression according to RECIST criteria is difficult to assess and could have accounted for the difficulty of the BICR to call disease progression in the bone[28]. These bone progression cases were reviewed with narratives and case report forms by the clinical review team and were thought to have been assessed appropriately by the investigator although it is not possible to rule out a level of bias. In addition there is an imbalance with respect to BICR assessment of progression events with investigator assessment of stable disease in the palbociclib plus letrozole arm compared to the letrozole alone arm (nine events vs. one). However there is less of a discrepancy with BICR assessing a progression event at an earlier time point than the investigator as this appears to be more balanced between arms.*

The discordance of events and censoring differences between the investigator and the BICR are concerning. Please see Dr. Erik Bloomquist's statistical review for a more detailed analysis of censoring and how discordance rates were determined. Dr. Bloomquist describes an early discordance rate between investigator and BICR censoring of 46.3% in the palbociclib plus letrozole arm vs. 50.8% in the letrozole only arm compared with a late discordance rate of 55.8% in the palbociclib plus letrozole arm vs. 33.3% in the letrozole alone arm. The pattern of this discordance could indicate

investigator bias. However, further sensitivity analyses and in depth review of individual cases was performed (see Section 6.1.11) reassuring the review team to the validity of the data and the activity of palbociclib.

Overall Survival:

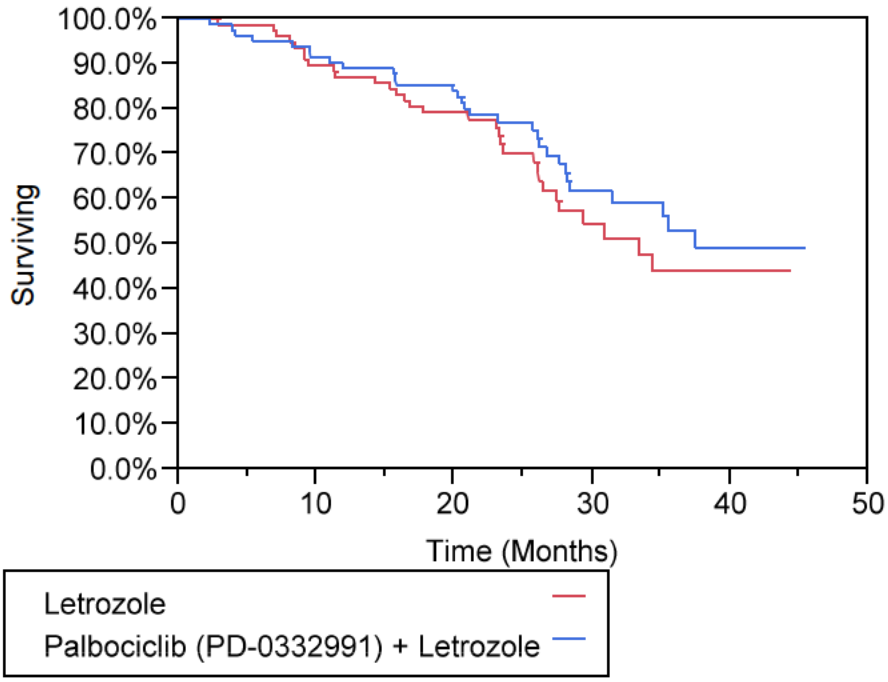
At the data cut off in November 2013, there were 61 deaths out of the total 165 patients. The median follow-up time was 29.6 months (95% CI: 27.9-36.0) in the palbociclib plus letrozole arm and 27.9 months (95% CI: 25.5-31.1) in the letrozole alone arm. The was not a statistically significant difference in overall survival between the two treatment arms although there was a trend toward improvement in the palbociclib plus letrozole arm. The HR was 0.813 (95% CI: 0.492-1.345; p=0.2105). The Overall Survival data is also shown in Table 28 and Figure 9.

Table 29: Overall Survival

	Phase 2 Part 1 and Part 2		**Part 1 N=66**		**Part 2 N=99**	
	Palbo + Letrozole N=84	**Letrozole N=81**	**Palbo + Letrozole N=34**	**Letrozole N=32**	**Palbo + Letrozole N=50**	**Letrozole N=49**
Deaths, n (%)	30 (35.7)	31 (38.3)	16 (47.1)	15 (46.9)	14 (28.0)	16 (32.7)
Median OS 95% CI	37.5 (28.4, NR)	33.3 (26.4,NR)	37.5 (27.6, NR)	33.3 (26.0, NR)	NR (26, NR)	NR (23.4, NR)
HR* 95% CI p- value	0.813 (0.492-1.345) 0.2105		0.844 (0.417-1.710) 0.3189		0.783 (0.382-1.606) 0.2520	

*stratified for Phase 2 combined and unstratified for Part 1 and Part 2.
NR: not reached
Source: CSR p155,Table 12.2.12.1.b

Figure 9: Overall Survival



Source: eesrv.xpt

***Reviewer Comment**: While there was not a statistically significant difference in overall survival the study was not powered to detect this difference with a low event rate and only 165 patients enrolled. Due to the multiple therapies available to breast cancer patients and the inclusion of crossover in many pivotal trials OS could be confounded. In this study although there was no crossover, 20-30% of patients received more than one line of subsequent therapy.*

Time-To-Progression:
Time-to-progression (TTP) in the ITT population was longer in the palbociclib plus letrozole arm (20.2 months median PFS) compared with the letrozole alone arm (10.2 months median PFS) with a HR of 0.399 (95% CI: 0.265-0.601; stratified log-rank p<0.0001). When the Part 1 and Part 2 cohorts were analyzed separately the results were consistent.

Objective Response Rate by Investigator:
Objective response rate (CR+ partial response) was assessed by the investigator and favored the palbociclib plus letrozole arm vs. the letrozole alone arm (42.9% [95% CI: 32.1-54.1] and 33.3% [95% CI: 23.2-44.7] respectively). The majority of the responses were partial with only one complete response in each arm.

Objective Response Rate by BICR:
Objective response rate was also assessed by the BICR. The objective response rate was 29.8% in the palbociclib plus letrozole arm vs. 21% in the letrozole alone arm.

Overall Tumor Response for Patients with Measurable Disease by Investigator:
For the ITT population investigator ORR for patients with measurable disease was 55.4% in the palbociclib plus letrozole arm compared with 39.4% in the letrozole alone arm. These results were consistent in the Part 1 and Part 2 cohorts of the study.

Overall Tumor Response for Patients with Measurable Disease by BICR:
Objective response rate was assessed by the BICR for the for patients with measurable disease and was 49% in the palbociclib plus letrozole arm compared with 32.7% in the letrozole alone arm.

Duration of Response:
In patients with either a complete or partial response to therapy as assessed by the investigator, the duration of response was longer in the palbociclib plus letrozole arm (20.3 months; 95% CI 13.4-25.8) compared to the letrozole alone arm (11.1 months;95% CI: 9.3-31.6).

Clinical Benefit Response:
The clinical benefit response rate (CR or partial response or SD ≥24 weeks) was 81% in the palbociclib plus letrozole arm and 58% in the letrozole alone arm with an odds ratio of 3.18 (5% CI: 1.48-6.98; stratified 1-sided p-value=0.0009) in favor of palbociclib plus letrozole.

Reviewer Comment*: The secondary response endpoints support the overall findings. The numeric increase in response rate in the palbociclib plus letrozole arm supports the activity of palbociclib.*

Patient-Reported Outcome:
The Modified Brief Pain Inventory Questionnaire (mBPI-sf) was employed for a secondary patient-reported outcome (PRO) endpoint. To qualify for inclusion in the endpoint patients had to complete over 50% of the questions at each cycle and end of treatment and 98% of patients were able to be included. The numeric score of pain severity was lower in the palbociclib plus letrozole arm and had a greater reduction from baseline than the letrozole alone arm until approximately Cycle 30 at which point the samples sizes became small. This study was undertaken in order to determine if palbociclib added to the commonly reported myalgias and joint pains seen with letrozole alone.

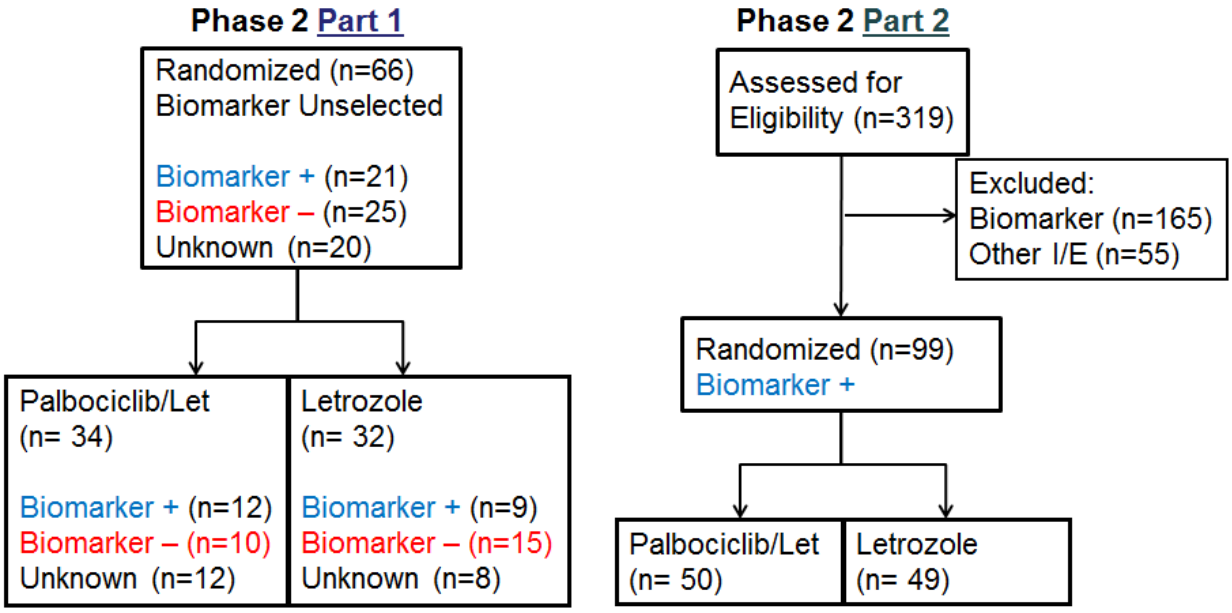
Reviewer Comment*: It is difficult to interpret PROs in the setting of an open-label trial. The mBPI-sf is not a comprehensive or sensitive PRO instrument however the results might suggest that palbociclib plus letrozole does not increase pain. Additional PRO instruments (FACT-B and EuroQol-5D) are being examined in the confirmatory trial PALOMA-2.*

Cell Cycle-Relevant Biomarkers:

As described in Section 5.3.1, the Phase 2 portion of PALOMA-1 was broken down into two Parts which differed based on biomarker status. Biomarker positive was determined by CCND1 amplification and/or *CDKN2A* loss. CCND1/CEP11 FISH ratio $\geq$ 1.5 translates into $\geq$ 3 copies of CCND1 gene in a diploid genome and was used as the cut-off for CCND1 amplification. The cut-off is on the lower end of published analyses of CCND1 gene amplification and thus per the applicant was chosen as such to be very inclusive and was based on the applicant's analysis of archived tissue samples with ER-positive Her2-negative advanced breast cancer. The applicant chose this low cut-off point in order to include ER+/HER2- advanced breast cancer patients with any potential for CCND1 amplification and planned on defining a more relevant cut-off value based on the data from Phase 2 with the "intent of confirming the predictive effect of this biomarker in Phase 3 study". The *CDKN2A* loss was determined by CDKN2A/CEP2 FISH ratio of <0.8 and was based on the average value resulting from enumeration of $\geq$ 20 tumor cell nuclei. A ratio of $\leq$ 0.5 represents heterozygous deletion. Other mechanisms resulting in gene expression or loss of expression such as transcription and translation regulation, or post transcription modification were not assessed (b) (4) .

The Part 1 cohort was an unselected patient population which had retrospective analysis of biomarker status. The Part 2 cohort was selected prospectively based on biomarker positive status (165 patients failed to screen positive for the biomarker) and all patients from that cohort were biomarker positive. See Figure 10 for a breakdown of biomarker status within the cohorts.

Figure 10: Biomarker status in the trial



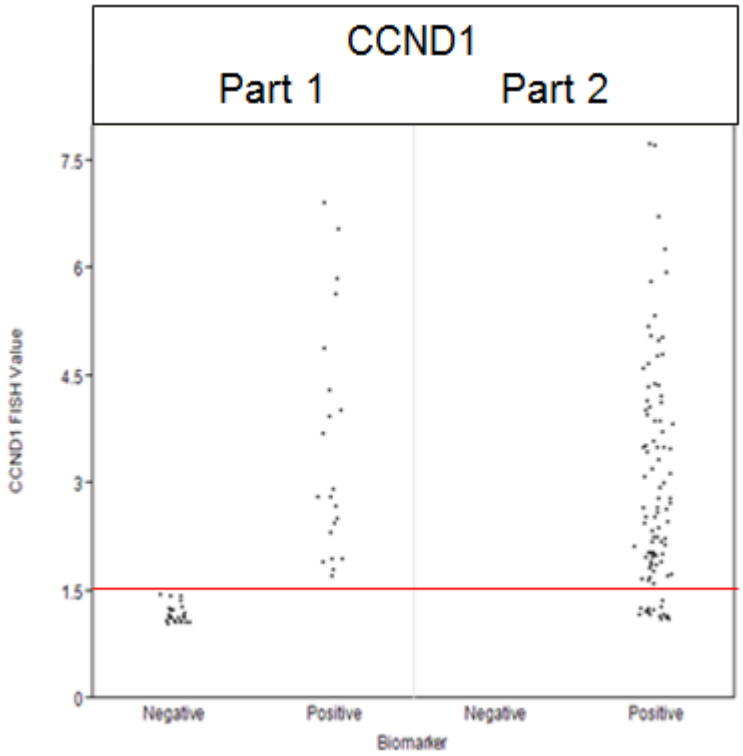
I/E: inclusion/exclusion criteria; Let: Letrozole
Source: CSR Table 14.1.1.1.b, 14.2.15.1.b, 14.2.15.1.2.b

There was a different distribution of biomarkers within the biomarker positive populations between Parts of the study. In Part 1 of the study there were 21 biomarker positive patients all of which had CCND1 amplification. Only 2 patients (9%) in Part 1 met criteria for *CDKN2A* loss (both in the letrozole alone arm). In Part 2 of the study, 31 patients from the palbociclib plus letrozole arm had CCND1 amplification alone, 11 had *CDKN2A* loss alone and 8 had a combination of CCND1 amplification and *CDKN2A* loss. In the Part 2 Letrozole alone arm, 36 patients had CCND1 amplification alone, four patients had *CDKN2A* loss alone and eight patients had a combination of CCND1 amplifciation and *CDKN2A* loss. The palbociclib plus letrozole had seven more patients with *CDKN2A* loss (n=19) compared to the letrozole alone arm in Part 2 of the study (n=12).

Across Parts of the study there was also differing distributions of FISH cut-off values. These distributions are graphically depicted in Figure 11A and 11B.

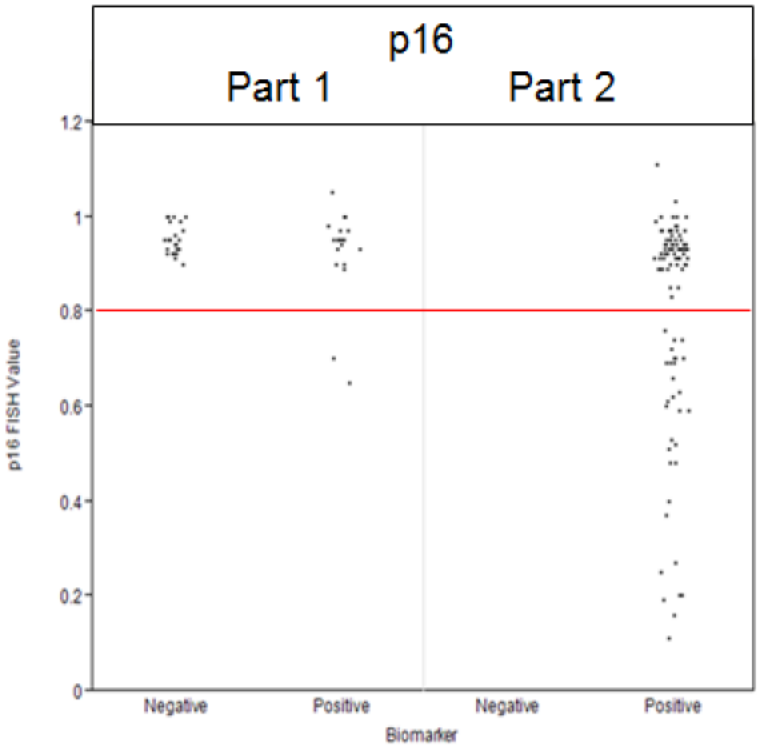
Figure 11: Distribution of FISH values across both parts of the study

A. CCND1 FISH values



CCND1 cut off for amplification ≥ 1.5 shown with the red line. Note that two patients fall in the upper range of the FISH values and thus are not depicted on this Figure.
Source: BMP.xls

B. CDKN2A FISH values



FISH cut off for *CDKN2A* loss <0.8 as depicted with the red line
Source: BMP.xpt

Analyses were performed examining PFS in Part 1 based on biomarker status. Results demonstrate that regardless of biomarker status, patients in the palbociclib plus letrozole arm had a longer median PFS then patients in the letrozole arm and this difference was more pronounced in the biomarker negative population (Table 29 and Figure 12).

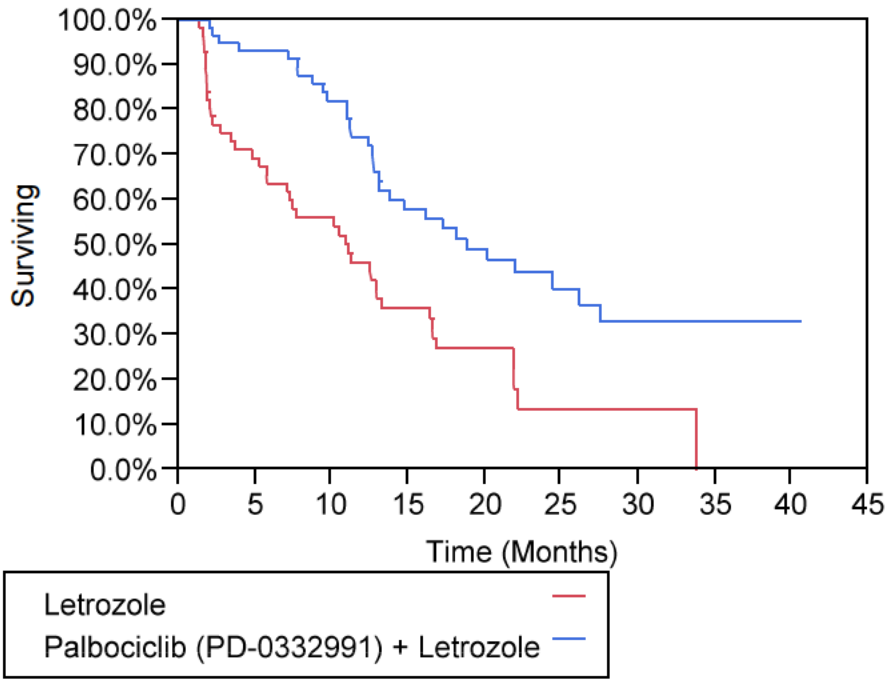
Table 30: Part 1 PFS by Biomarker status

	Biomarker Positive		**Biomarker Negative**	
	Palbo + Let	**Letrozole**	**Palbo + Let**	**Letrozole**
Number of Patients	12	9	10	15
Median PFS (months) **95% CI**	26.1 (11, NR)	7.5 (1.8, 16.8)	35.3 (8.1, NR)	5.7 (2.1, 10.5)
HR **95% CI** **p value (when n≥10 in both arms)**	0.2 (0.07, 0.71)		0.2 (0.07, 0.71) 0.006	

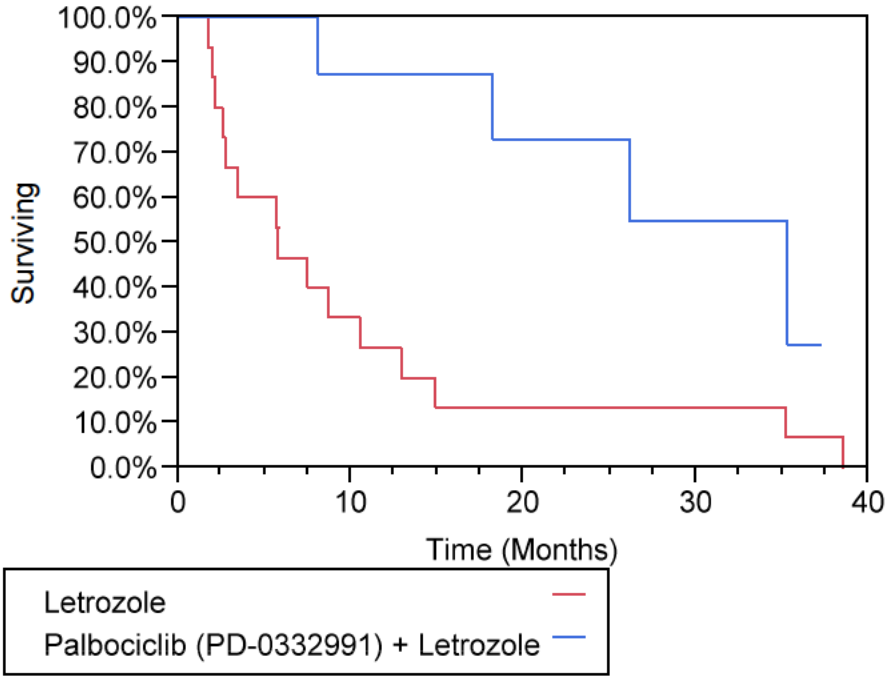
Source: BMP.xpt and eesrv.xpt

Figure 12: KM Curve of Part 1 broken down by biomarker status

A. Biomarker Positive



B. Biomarker Negative



Source: BMP.xpt and eesrv.xpt

***Reviewer Comment**: While the biomarker positive population as definied by the applicant represented 73% (n=120) of the patients in the Phase 2 combined Part ITT*

population, there was a wide distribution of the cut-offs and the cut-off for CCND1 which accounted for the majority of biomarker positive calls was low and more inclusive. For these reasons and the fact that exploratory analyses demonstrate the maintained benefit on PFS of palbociclib plus letrozole regardless of biomarker the unselected patient population indication appears acceptable. However, given some of the exploritory analyses performed by the clinical and statistical review team (see Section 6.1.8) it appears that further analysis in the Phase 3 confirmatory study to identify a biomarker population that may be predictive of palbociclib benefit is merited.

Additional analyses examining Ki67 and CYP19A1 and CCND1 genotypes were conducted. No statistically significant difference in PFS between Ki67 (≤ or >20%), CYP19A1 (wild-type vs. mutant) genotypes or CCND1 (wild-type vs. mutant) genotypes were seen. A more detailed description of these analyses can be found in the pharmacogenomics review by Dr. Rosane Charlab Orbach.

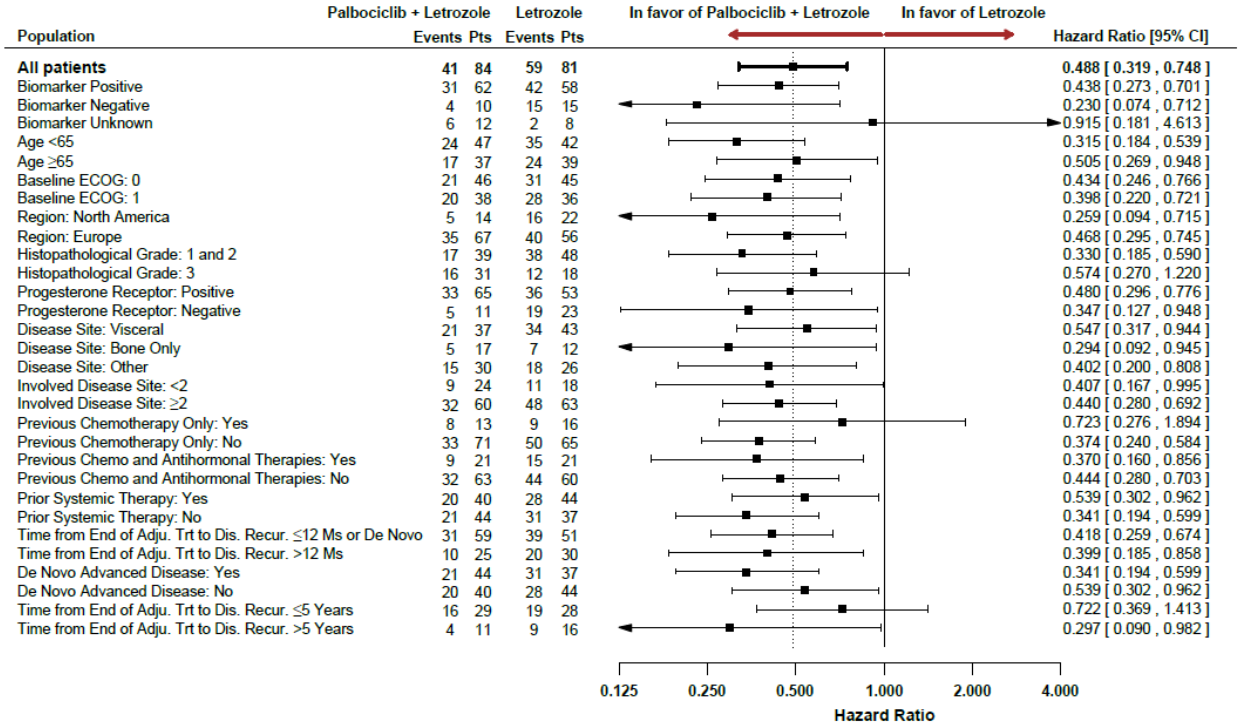
6.1.7 Other Endpoints

Not applicable.

6.1.8 Subpopulations

Multiple subpopulations were examined, including subgroups by biomarker, age, region, grade, stratification factors, and prior treatment. The forest plots of the subgroups analyses of PFS are shown in Figure 13.

Figure 13: Primary and Subgroup Analyses of Investigator-Assessed Progression-Free Survival with Stratification Factors per CRF: Intent-to-Treat Population (Applicant Figure)



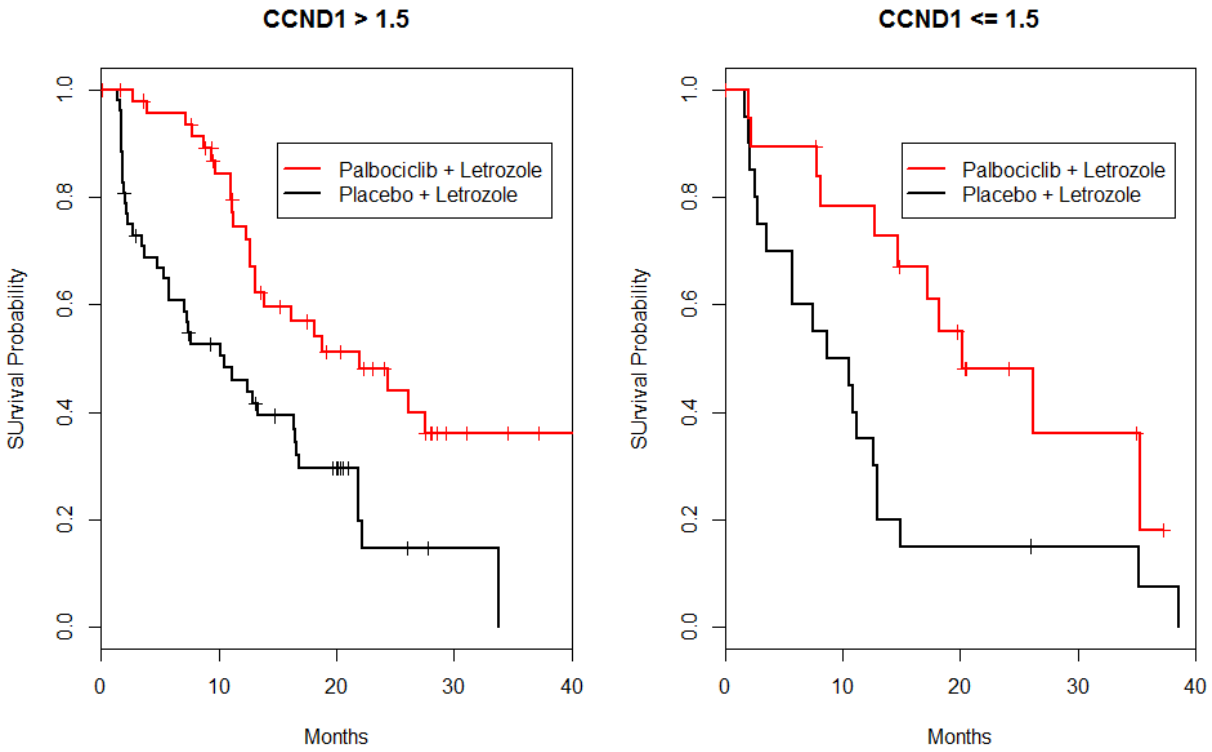
Abbreviations: Adju=Adjuvant; CI=Confidence interval; CRF=Case report form; Dis=Disease; ECOG=Eastern Cooperative Oncology Group; ITT=Intent-to-treat; Pts=Patients; Recur=Recurrence; Trt=Treatment.
Source: CSR Page 150, Table 14.2.13.2.b

Reviewer Comment: *In the majority of the subgroups the HR and CIs are preserved supporting the overall conclusions of the study. In some cases such as prior chemotherapy without hormonal therapy and biomarker unknown status the spread of the confidence interval is broad due to a small number of patients. No subgroups demonstrate a detriment of palbociclib plus letrozole.*

Biomarker:

The review team performed multiple analyses using various biomarker cut-offs. For CCND1, the benefit in median PFS appeared to remain constant regardless of the cut off used. In the CCND1 >1.5 group, the HR was 0.408 (95% CI: 0.242, 0.686) favoring the palbociclib plus letrozole arm with an improvement in median PFS from 10.4 months to 21.9 months (see Figure 14). In the CCND1<1.5 group the HR was 0.418 (95% CI: 0.218, 0.803) favoring the palbociclib plus letrozole arm with an improvement in median PFS from 8.7 months to 20.1 months. Further analyses (not shown) indicated a similar preservation of palbociclib plus letrozole benefit on PFS using ratios of $\geq$ 2, $\geq$ 3, and $\geq$ 4 for CCND1 amplification.

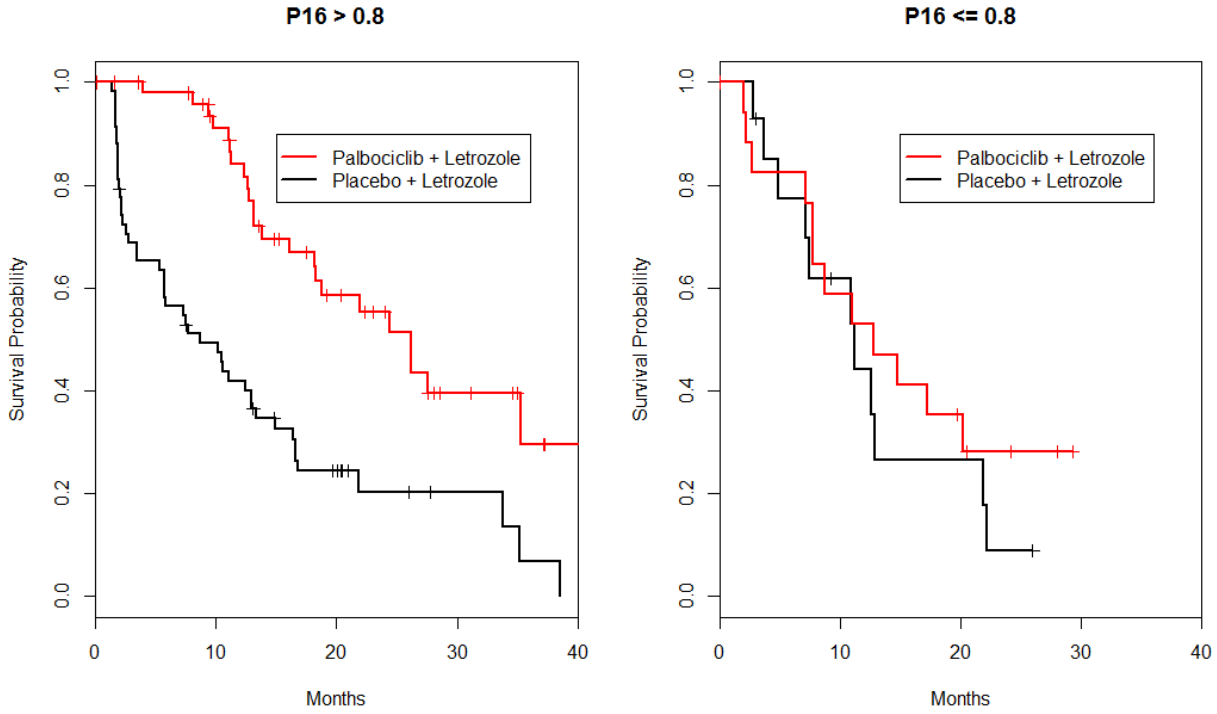
Figure 14: KM curve for PFS by CCND1 cut-off ratio of 1.5 (Statistical Reviewer Figure)



Source: BMP.xpt and eedrsp.xpt

When an analysis was performed examining PFS by *CDKN2A* loss or gain the results did not demonstrate a palbociclib plus letrozole PFS benefit for the *CDKN2A* loss population (see Figure 15). In the *CDKN2A* >0.8 group the HR was 0.315 (95% CI: 0.189, 0.523) favoring the palbociclib plus letrozole arm with an improvement in median PFS from 8.7 months to 26.1 months. In the *CDKN2A* <0.8 group the HR was 0.793 (95% CI: 0.387, 1.624) with median PFS 11 vs. 11.2 months in the palbociclib plus letroole arm vs. the letrozole alone arm respectively.

Figure 15: KM curve for PFS by CDKN2A cut-off ratio of 0.8 (Statistical Reviewer Figure)



Source: BMP.xpt and eedrsp.xpt

Rb negative breast cancer cell lines have been shown to demonstrate resistance to palbociclib, however HR positive luminal A breast cancers typically do not exhibit Rb loss and only four patients (out of 80 samples tested) had Rb loss in this study [21,22]. These four patients (two on each arm) did not have a detectable difference in median PFS.

Reviewer Comment*: The results described above are ad hoc and exploratory with low sample size however it appears that CDKN2A loss may predict a level of resistance to palbociclib. This finding is paradoxical given the current knowledge of the Rb pathway and prior pre-clinical work [21,22]. However resistance to palbociclib was seen in another study in six out of nine glioblastoma cell lines with CDKN2A deletion[29]. Compensatory INK family expression (such as p18) might partially account for some resistance but does not fully explain these findings. There are many mechanisms for gene over-expression and loss of expression; PALOMA-1 only examined gene amplification and deletion. Further analysis is warented and the clinical post marketing commitment is meant to address the better detection of a predictive biomarker.*

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose and schedule of letrozole used in Study A5481003 represents the standard dose and schedule used in the advanced breast cancer setting and reflected in the approved product labeling. Please see the Clinical Pharmacology Review for a discussion of palbociclib dosing.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

These issues are addressed throughout the efficacy review given that the primary endpoint of the trial is a time to event endpoint

6.1.11 Additional Efficacy Issues/Analyses

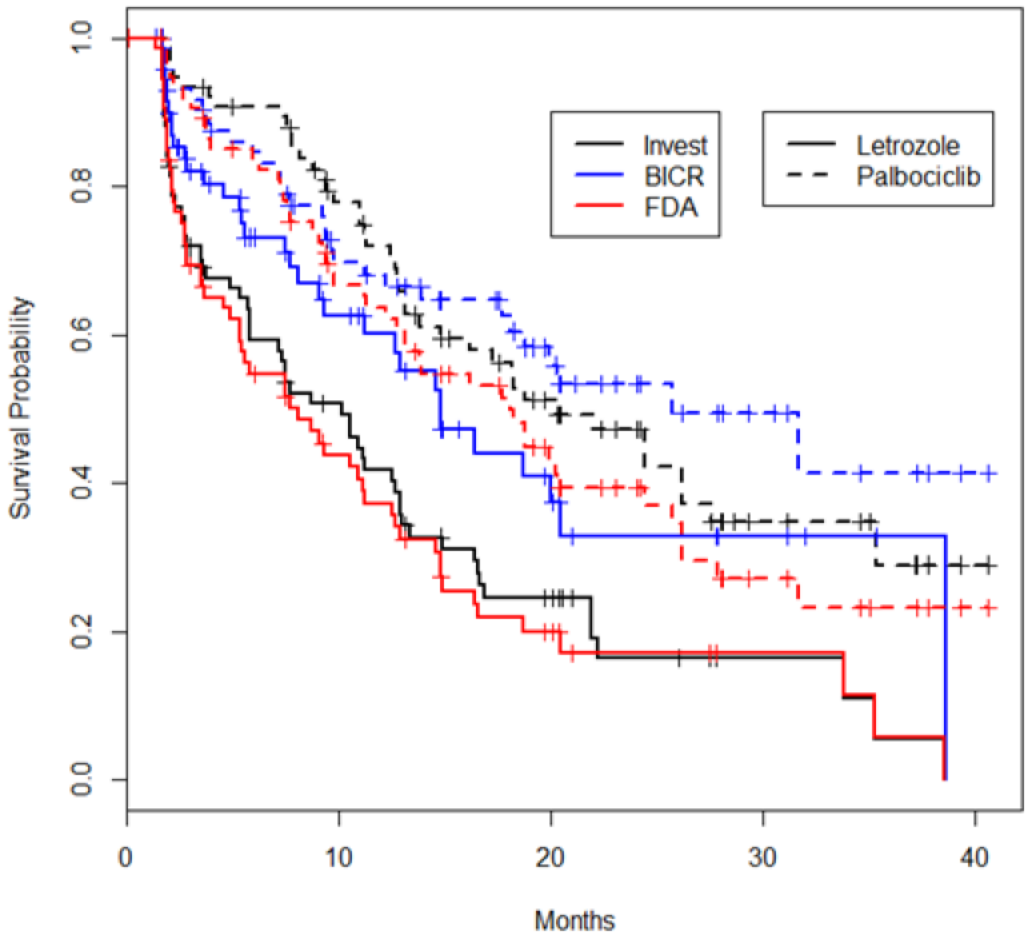
A number of sensitivity analyses were conducted by the FDA clinical and biostatistical reviewers. Those most pertinent to the recommended regulatory action are presented below.

The first sensitivity analysis relied upon combined data from the investigator assessment and the BICR as decided by the review team going over each case of discordance in detail. Ninety six cases where the investigator and the BICR disagreed with respect to type of event or censor, date of event or censor, or event or censor reason were identified. Each of these 96 cases was examined by the review team in a blinded fashion based on the data available to FDA including a review of the narrative, case report form, radiology written report (if available), BICR adjudication, and datasets. The review team made determinations based on each of these cases regarding agreement or disagreement with the investigator assessment. In most cases, the review team agreed with the event to be progressive disease (PD) based on the earliest PD assessment (either by the investigator or the BICR). Per FDA's analysis the median PFS in the palbociclib plus letrozole arm was 18.1 months and in the letrozole alone arm was 8.1 month (HR 0.576) as shown in Table 30. The results were consistent with the primary analysis and fell in-between the BICR and investigator-assessed PFS results as shown in Figure 16 with all three analysis showing a 10 month improvement in median PFS.

Table 31: FDA Analysis, ITT Population

	Palbociclib + Letrozole N=84	Letrozole N= 81
FDA Agreement with		
• **Investigator**	59 (70.2%)	62 (76.5%)
• **BICR**	60 (71.4%)	51 (62.9%)
• **both simultaneously**	36 (42.9%)	33 (40.7%)
Median PFS, months (95% CI)	18.1 (12.2, 24.4)	8.1 (4.8, 11.2)
HR (95% CI) p-value	0.576 (0.378, 0.870) 0.009	

Figure 16: KM Curve FDA analysis with Investigator and BICR, ITT population (Statistical Reviewer Figure)



Invest: investigator-assessed; FDA: FDA review team assessment
Source: narratives, onn1.xpt, tmmp.xpt, ptevnt.xpt, eedrsp.xpt

An additional sensitivity analysis based on progression of bone disease was performed. Of the 96 patients above, 42 cases called by the investigator as progression were considered stable disease by BICR (26 on the letrozole alone arm and 16 on the palbociclib plus letrozole arm). Of those 42 cases, 20 were related to progression based on bone disease (14 on the letrozole only arm and 6 on the palbociclib plus letrozole arm). When these 20 patients were censored at the time they were considered progressive disease by the investigator the improvement in median PFS from the palbociclib plus letrozole arm to the letrozole alone arm was 14.7 to 10.1 months respectively with a HR of 0.703 (95% CI: 0.445, 1.105).

We also conducted an additional "worst case" analysis of PFS, in which patients who discontinued treatment without a documented PFS event were censored in the control arm but were classified as having had a PFS event in the palbociclib plus letrozole arm. In this worst case analysis of PFS using the investigator data, the hazard ratio favors the palbociclib plus letrozole arm as shown in Table 31 below.

Table 32: FDA, Worst Case Analysis of PFS, ITT Population

	Palbociclib + Letrozole N=84	**Letrozole N= 81**
PFS events, n (%)	65 (77%)	59 (73%)
Median [95% CI], months	13.1 (11, 17.5)	10.2 (5.7, 12.6)
HR (95% CI)	0.793 (0.546, 1.152)	

Reviewer Comment: *The results of these sensitivity analyses support the robustness of the primary efficacy analysis.*

Additional sensitivity analyses were run to reassure the reviewers regarding investigator and financial interests. When the sites with the investigators disclosing financial interest in the outcome of the study were removed individually from the analysis population or removed all together the benefit of palbociclib remained (see Table 32).

Table 33: Sensitivity analyses by sites with financial disclosure

Site #	Palbociclib Event	Palbociclib No Event	Letrozole Event	Letrozole No Event	Total Patients Per Site	HR* Excluding Site(s)
(b) (6)	2	3	4	0	9	0.478
	1	1	1	2	5	0.477
	3	1	0	1	5	0.475
	0	3	2	0	5	0.519
	2	1	0	1	4	0.471
	1	0	1	2	4	0.495
All above	9	9	8	6	32	0.498 0.404#

*stratified; #unstratified
Source: eedrsp.xpt

In addition, if the 32 patients who were enrolled at these sites with investigator financial interest were analyzed by the BICR assessment the HR remained at 0.491 (95% CI 0.313, 0.772) with an improvement from 11.1 months to 24.4 months in the letrozole and palbociclib plus letrozole arm respectively.

Similarly given the issues with the site inspection of Dr. Finn's site 1001, a sensitivity analysis was performed removing this site from the analysis and the HR remained consistent at 0.507 (95% CI: 0.331, 0.776).

***Reviewer Comment**: The sensitivity analysis regarding financial information and site inspection issues supports the primary analyses based on ITT patients.*

The final sensitivity analysis performed was related to the misclassification of stratification factors used for randomization. As these factors differed in many cases from what was reported in the CRF, the study arms were imbalanced with respect to disease site and disease free interval. See Section 6.1.3 for a full description of the treatment imbalances. Given this finding the review team performed an unstratified analysis finding a HR of 0.41 (0.32-0.56) and a stratified analysis based on the CRF data which found a HR of 0.46 (0.30-0.70).

***Reviewer Comment**: These sensitivity analyses support the primary analysis based on ITT patients and support the overall conclusion of palbociclib plus letrozole benefit.*

7 Review of Safety

Safety Summary

In this NDA, the Applicant submitted safety data for 755 patients/subjects (industry-sponsored clinical studies) (original submission, 29 November 2013). This included 297 healthy subjects and 458 patients with malignant disease. The clinical safety data

supporting this NDA is primarily derived from the Phase 1/2 Study A5481003 or PALOMA-1 (Phase 1, N=12, Phase 2, N=83).

Key safety findings from PALOMA 1 (A5481003), and from the supportive safety database:

- **Deaths**: There were no deaths on-study in the Phase 1 part of PALOMA-1. As of 29 November 2013, 1 of 83 patients in the palbociclib plus letrozole arm and 0 of the 77 patients in the letrozole alone arm died on-study (within 28 days of the last dose) in the Phase 2 part of PALOMA-1. Per investigator assessment this one death was considered due to disease progression.

- **Serious Adverse Events (SAE), Discontinuations and Dose Modifications**: In the Phase 1 portion of PALOMA-1, two patients had SAEs (pulmonary embolism and pain); neither of the SAEs were considered by the investigator to be treatment-related or resulted in permanent or temporary discontinuation of study treatment. In the Phase 2 part of PALOMA-1, 18 patients (21.7%) who received palbociclib plus letrozole, and 5 patients (6.5%) who received letrozole experienced SAEs. One was considered treatment-related SAE (Colitis ischemic). In addition, there were more AEs leading to permanent discontinuation (14.5% palbociclib plus letrozole, 2.6% letrozole alone).

- **Grade 3 and 4 Adverse Reactions:** There were higher grade 3-4 adverse reactions on palbociclib plus letrozole arm compared to the letrozole alone arm (77.1% vs. 20.8%). One patient in the palbociclib plus letrozole arm had a grade 5 Treatment-Emergent Adverse Event (TEAE) (due to disease progression).

- **Common Adverse Reactions:** In Phase 2 part of PALOMA-1, the common TEAEs (i.e., ≥20% of patients) in the palbociclib plus letrozole arm were Neutropenia (74.7%), Leukopenia (43.4%), Fatigue (41.0%), Anemia (34.9%), Nausea (27.7%), Arthralgia (22.9%), Hot flush (22.9%), Alopecia (21.7%), and Diarrhea (20.5%); while the most frequently reported TEAE in the letrozole alone arm was Fatigue (23.4%).

- **Neutropenia:** Neutropenia was the most frequently reported TEAE (Phase 1: 91.7%; Phase 2: 75.9% (49.4% with Grade 3 and 6% with Grade 4) in patients who received palbociclib plus letrozole in Study 1003. No cases of febrile neutropenia, neutropenic sepsis, or neutropenic infection were reported in PALOMA-1.

- **Infections:** A higher rate of infections was observed in the palbociclib plus letrozole arm (55.4%) than in the letrozole alone arm (33.8%). There were no cases of febrile neutropenia or discontinuations from study treatment due to an infection-related event in PALOMA-1.

- **Eye Disorders:** A higher rate of Eye Disorders was observed in the palbociclib plus letrozole arm (20.5%) than in the letrozole alone arm (5.2%).Total Eye disorders includes the following PTs: Blindness, Cataract, Conjunctivitis Diplopia, Dry eye, Eye irritation, Eye pruritus, Eye swelling, Lacrimation increased, Photophobia, Vision blurred, Visual acuity reduced Visual impairment, Vitreous floaters

- **Pulmonary Embolism:** A numerical increased rate of pulmonary embolism was observed in the palbociclib plus letrozole arm (4.8%) than in the letrozole alone arm (0%). In addition there was one case of pulmonary embolism seen in Phase 1 part of PALOMA-1 (N=12).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical safety data supporting this NDA is primarily derived from the Phase 1/2 study PALOMA-1 (A5481003). Table 33 outlines the safety studies submitted to the NDA, as well as the data cut-offs for initial submission and 120 day safety update.

Table 34: Summary of Safety Populations submitted to NDA

Study [A]	Design	Population	N	Status	Cut-off (NDA)	Cut-off (120 day)
Study A5481001	Phase 1	Advanced cancers	74	Completed	12 June 2008	01 June 2014
Study A5481002	Phase 1b	Relapsed/Refractory Mantle Cell Lymphoma	17	Completed	10 September 2012	N/A
Study A5481003	Phase 1/2 R	Advanced Breast Cancer	95	Completed	29 November 2013	15 April 2014
Study A5481004	Phase 1/2	Refractory Multiple Myeloma	51	Completed	15 November 2013	N/A
Study A5481008[B]	Phase 3 R	Advanced Breast Cancer	126	Ongoing	29 November 2013	01 June 2014
Study A5481010	Phase 1	Japanese Advanced Solid Tumor	18	Ongoing	29 November 2013	01 June 2014
Study A5481023 [B]	Phase 3 R	Advanced Breast Cancer	227	Ongoing	N/A	01 June 2014

A: Healthy Volunteer Studies and Investigator-Initiated Research Studies are not included in this Table.
B: Blinded therapy
Source: modified Table 3, 5 and 10 (Summary Clinical safety, page 26, 28 and 56) and 120 day safety update (Table 2, Page 23 and 24)

7.1.2 Categorization of Adverse Events

The Applicant defined adverse events (AEs) as any untoward medical occurrence in a clinical investigation subject administered a product or medical device, with or without a causal relationship with the treatment or usage.

An abnormal objective test finding was reported as an AE if the test result was associated with accompanying symptoms, and/or required additional diagnostic testing or medical/surgical intervention, and/or led to a change in dosing or discontinuation from the trial, significant additional concomitant drug treatment or other therapy, and/or was considered to be an AE by the investigator or the Applicant.

Reviewer Comment: *This definition of AE led to the under reporting of many of abnormal laboratory findings and possibly other types of abnormal subjective and objective findings in the patients.*

All AEs and SAEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA). Individual CSRs used the version of MedDRA that was current at the time they were written (Version 11.0 for Study 1001 [except SAEs which used Version 11.1]); Version 13.0 for Study 1002; Version 16.0 for Study 1004 and Version 16.1 for Study 1003). Ongoing Studies 1008, 1010, and the IIR studies used Version 16.1.

AEs were summarized by MedDRA primary system organ class (SOC), and by Preferred term (PT). The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 was used for Studies 1001, 1002, 1003, and 1004 and Version 4.0 was used for Study 1010.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In total, with the August 13, 2014 NDA submission, the Applicant submitted safety data for 755 patients/subjects (industry-sponsored clinical studies). This included 297 healthy subjects and 458 patients with malignant disease. Of the 458 patients with malignant disease, 255 received at least 1 dose of palbociclib either as a single agent or as a component of combination therapy, and 77 received a comparator. In addition, 126 patients were randomized to ongoing Study A5481008; the data from the 2 treatment arms (palbociclib plus letrozole and placebo plus letrozole) are pooled under “blinded therapy”. As of the 29 November 2013 data cutoff date, 101 female patients with ER-positive, HER2-negative advanced breast cancer received 125 mg palbociclib in combination with 2.5 mg letrozole (Study A5481003 [N=95] and Part 2 of Study A5481010 [N=6]).

In addition, the Summary of Clinical Safety of palbociclib included in the NDA contained 10 Investigator-Initiated Research (IIR) studies (palbociclib single-agent and combination studies in patients with breast cancer or other malignant solid tumors) were ongoing or completed as of the November 29th, 2013 data cutoff date. Approximately 229 patients were enrolled in these IIR studies as of that data cutoff date.

On November 21st, 2014, the Applicant submitted the 120 day safety update report. The Applicant has chosen two cutoff dates for 120 day safety update. The rationale is stated as the earlier data cutoff date (April 15th, 2014) for the pivotal Study A5481003 was chosen to accommodate the additional time needed to fully analyze and reconcile safety information from the clinical database and the safety database. In order to present more current safety information from the safety database on serious adverse events, including deaths, reported in the remaining studies summarized in the safety update, a later data cutoff date (June 1st, 2014) was chosen.

Safety data summarized in the 120 day safety update comprise those from a total of 1029 patients with malignant solid tumors participating in five industry-sponsored completed and ongoing clinical studies. Of these five studies, four were originally included in the Summary of Clinical Safety (Studies A5481001, A5481003, A5481010, and A5481008). In addition, a new ongoing trial in patients with metastatic breast cancer, Study A5481023, was included in the safety update. (Study A5481023: Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Fulvestrant (Faslodex) With or Without PD-0332991 (Palbociclib) ± Goserelin in Women With Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy)

Studies A5481002 and A5481004 in patients with malignant disease other than breast cancer were not included in the 120 day safety update. These completed studies were reviewed in the SCS as of November 29th, 2013, and no patients were ongoing at that data cutoff date. Overall, safety database for the industry-sponsored palbociclib clinical development program summarized in the safety update was expanded by 712 patients with advanced breast cancer (all receiving blinded treatment in the ongoing Studies A5481008 and A5481023) since the SCS data cutoff date of November 29th, 2013.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Exposures Phase 2

Exposure to palbociclib plus letrozole and letrozole in Phase 2 part of PALOMA-1 is summarized in Table 34 below.

In the Phase 2 portion (Part 1 and Part 2), the median daily dose of palbociclib was 125.0 mg (range: 79.6 mg to 266.7 mg). The median daily dose of letrozole was 2.5 mg (range: 2.5 mg) in both the palbociclib plus letrozole arm and the letrozole alone arm.

Table 35: Drug Exposure and Dose Intensity– Phase 2: As Treated Set

	Phase 2 (Ph2P1+Ph2P2)			Ph2P1			Ph2P2		
	Palbo+ Let (N=83)		Let (N=77)	Palbo+ Let (N=33)		Let (N=29)	Palbo+ Let (N=50)		Let (N=48)
	Palbo	Let		Palbo	Let		Palbo	Let	
Median treatment duration (days)	420	428	231	416	416	166	431	438.5	335.5
Dose reduction (%)	33 (39.8)	-	-	16 (48.5)	-	-	17 (34.0)	-	-
Dose interruption (%)	47 (56.6)	32 (38.6)	23 (29.9)	22 (66.7)	11 (33.3)	7 (24.1)	25 (50.0)	21 (42.0)	16 (33.3)
Mean Cumulative dose	41691.9	1254.9	843.8	45258.3	1399.8	804.1	39338.0	1159.3	867.8
Median Cumulative dose	37750	1070	577.5	35950	1040	415	38462.5	1096.3	831.3
Mean Relative dose intensity (%)	94.1	99.5	99.5	88.2	99.5	99.7	98.0	99.6	99.3
Median Relative dose intensity (%)	95.4	100	100	88.8	100	100	99.3	100	100

Palbo: palbociclib; Let: letrozole; Ph2P1: Phase 2 Part 1; Ph2P2: Phase 2 Part 2
Source: Table 66 and 67 CSR PALOMA study, page 228

The median duration of palbociclib exposure in the Phase 1 part of the study was approximately 13.8 months. The median duration of letrozole exposure in the Phase 1 part of the study in the palbociclib plus letrozole arm was 14.1 months. The median exposure duration in the letrozole alone arm of the total Phase 2 population was 7.6 months (120 day safety update).

Demographics:
See Section **Error! Reference source not found.**

7.2.2 Explorations for Dose Response

Please see Clinical Pharmacology/Pharmacometrics Reviews by Drs Ping Zhao, Jerry Yu, Rosane Charlab Orbach, and Jeanne Fourie Zirkelbach.

7.2.3 Special Animal and/or In Vitro Testing

See Pharmacology/Toxicology review by Dr. Wei Chen.

7.2.4 Routine Clinical Testing

In PALOMA-1, routine laboratory analyses (including hemoglobin, WBC, neutrophils, lymphocytes, platelet count. BUN (or urea), creatinine, albumin, AST/ALT, total bilirubin, alkaline phosphatase, LDH, sodium, potassium, calcium, magnesium, phosphorous, uric acid) were obtained at screening (≤28 day prior to dosing), Day 1 and 14 of cycles 1 and 2 and day 1 of cycles ≥3 and end of treatment visit.

Physical Examination included an examination of major body systems (at screening and on Day 1 of each cycle), height (at screening only); weight, blood pressure and pulse rate (on Day 1 of each cycle).

Vital signs, urine pregnancy test, and physical exams were obtained at screening (-30 to -1), during each cycle, and at the study drug completion visit (30 days +/- 7 after last dose of study drug).

Scheduled three consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine the mean QTc interval.

Arm A: on Day 1 of Cycles 1 and 3; and on Day 14 of Cycles 1 and 2,
Arm B: on Day 1 of Cycles 1, 2, and 3.

Reviewer Comment: *Pregnancy test, urinalysis and INR and aPTT were not collected in the study.*

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Palbociclib is a selective, reversible, small molecule inhibitor of CDK 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. There are no other similar drugs in this drug class on the market. Adverse events associated with reduced cellular proliferation may include myelosuppression, GI toxicity, fatigue and alopecia.

7.3 Major Safety Results

7.3.1 Deaths

Deaths in the pivotal study 1003 (PALOMA-1): There were no deaths on-study in the Phase 1 portion of PALOMA-1. As of November 19th, 2013, one of 83 (1.2%) patients

(Subject ID: 11183017) in the palbociclib plus letrozole arm and zero of the 77 (0%) patients in the letrozole alone arm died on-study (within 28 days of the last dose) in the Phase 2 portion. This death is summarized below.

Subject 11183017, a 59-year-old White woman from Ukraine who received 125 mg palbociclib plus 2.5 mg letrozole until Day 68 died due to disease progression, which was considered to be unrelated to study treatment.

There were no additional deaths reported with the 120 day Safety update (April 15th, 2014).

Deaths in the Industry-sponsored Clinical Studies:

There were a total of 12 deaths on-study (after the first dose of study drug and within 28 days of the last dose of study drug [30 days in Study A5481001]) in industry-sponsored clinical studies; 11 patients received palbociclib and one received blinded therapy (Table 35).

Table 36: Summary of Deaths On Study (On Treatment or Within 28 Days of Last Dose) – Industry-Sponsored Palbociclib Clinical Studies

Study	Population	N Deaths	Total N subjects
Study A5481001[A]	Advance cancers	7	74
Study A5481002	Relapsed/Refractory Mantle Cell Lymphoma	1	17
Study A5481003	Advanced Breast Cancer	1	95
Study A5481004	Refractory Multiple Myeloma	2	51
Study A5481008[B]	Advanced Breast Cancer	1(blinded)	126
Study A5481010	Japanese Advanced Solid Tumor	0	18
Other	Healthy Volunteer Studies [C]	0	297

A: deaths were reported up to and including 30 days after the last administration of study drug, in other studies on Treatment or Within 28 Days of Last Dose
B: blinded therapy
C: Healthy Volunteer Studies include: Studies A5481009, A5481011, A5481012, A5481015, and A5481017. A5481018, A5481020, A5481021, A5481022, A5481026, and A5481036.
D: IIRS: Investigator-Initiated Research Studies
Source: modified Table 47 (Summary Clinical safety, page 114)

Deaths in the Investigator-Initiated Research (IIR) Studies:

There were no deaths in patients receiving palbociclib monotherapy or in combination with chemotherapy or non-chemotherapy in breast cancer studies as of the November 29th 2013 data cutoff date.

Eleven patients had events with a fatal outcome in studies of single-agent palbociclib in non-breast cancer solid tumors. The events with a fatal outcome were disease progression (n=8), cardiac arrest (n=1), death (n=1 [unknown cause of death]), and lung infection (n=1). The fatal events were assessed as related to study treatment in two cases (Case 2011273560 and Case 2011033731). An additional four patients died, but did not have an event with a fatal outcome reported. The events reported in the cases for these four patients were Grade 3 febrile neutropenia (Case 2011042267), Grade 3 fall and Grade 2 back pain (Case 2013272871), urinary tract infection and deep vein thrombosis (Case 2013281179 [no grade provided]), and Grade 3 meningitis, Grade 3 headache, and Grade 1 cerebrospinal fluid leakage (Case 2011125366). Of these events, Grade 3 febrile neutropenia was considered related to treatment. Two of the four patients died of disease progression (Cases 2013272871 and 2011125366). The cause of death was not provided for the other two patients; however, the patient in Case 2011042267 had discontinued the study 63 days prior to death due to clinical progression and the patient in Case 2013281179 permanently discontinued the study in response to the events 21 days prior to death.

Reviewer Comments: *The majority of the deaths (eight out of 11 cases) appear to be due to disease progression.*

7.3.2 Nonfatal Serious Adverse Events

Phase 1 Part of Study A5481003

In the phase 1 portion of PALOMA-1 (A5481003), two patients had SAEs; neither of the SAEs were considered by the investigator to be treatment-related or resulted in permanent or temporary discontinuation of study treatment:

Patient 10011002:
A 68-year-old White female, had an SAE of **Grade 4 Pulmonary embolism** that was detected during routine CT scanning performed on Study Day 773 (Day 32 of Cycle 25). The patient was asymptomatic. No action was taken with respect to palbociclib or letrozole. The event resolved on Study Day 795 and was considered by the investigator to be unrelated to palbociclib or letrozole.

Patient 10011008:
A 68-year-old, Caucasian female subject started receiving palbociclib on July 27th, 2009 on a 3/1 schedule and oral letrozole 2.5 mg daily on August 7th, 2009. On December 21st, 2009, the subject called clinic complaining of severe pain on left side in the

abdominal area, just below ribs and above hip bone. The subject was prescribed ciprofloxacin 500 mg twice daily for 3 days as infection prophylaxis. The subject was told to follow up in clinic or with primary care physician if pain persisted. The subject went to emergency room on (b) (6) with similar complaint and on the same day she was admitted. A CT scan of the lumbar spine revealed a pathologic fracture of the left aspect of the L2 vertebral body. No action was taken with study drugs. Therapeutic measure taken to treat the event included a cortisone injection. The subject was discharged on (b) (6)

There were two additional cases of SAEs (Grade 3 nausea and vomiting) reported with the 120 day Safety update (15 April 2014) for the same two patients, none were reported to be fatal or treatment-related.

Phase 2 Part of Study A5481003

In the phase 2 part of PALOMA-1 (A5481003), as of the November 29th, 2013 data cut-off date, 18 patients (21.7%) who received palbociclib plus letrozole, and 5 patients (6.5%) who received letrozole experienced Serious Adverse Events (SAEs). Table 36 highlights the SAEs by preferred term.

There was only one treatment-related SAE reported in the Phase 2 part of the study. In the palbociclib plus letrozole arm, one patient (1.2%) had a treatment-related SAE (Colitis ischemic, Patient 10913002).

Table 37: SAE preferred terms in either treatment Arm (All Causalities) – Phase 2 A5481003: As Treated Set (as of 29 November 2014)

MedDRA Preferred Term	Palbociclib + Letrozole N=83		Letrozole N=77	
	Grade 1/2 N	Grade 3/4 N	Grade 1/2 N	Grade 3/4 N
Pulmonary embolism	0	3*	0	0
Back pain	0	1	0	0
Diarrhea	0	2	0	0
Abdominal pain		1	0	0
Alanine aminotransferase increased	1	0	0	0
Aspartate aminotransferase increased	1	0	0	0
Asthenia	1	0	0	0
Blood alkaline phosphatase increased	1	0	0	0
Bone pain	0	1	0	0
Chest pain	0	1	0	0
Colitis ischemic	0	1	0	0
Disease progression	0	1	0	0
Fallopian tube cancer	0	1	0	0
Fractured sacrum	0	1	0	0
Gamma-glutamyltransferase increased	0	1	0	0
Gangrene	0	1	0	0
Gastrointestinal disorder	0	1	0	0
Humerus fracture	0	1	0	0
Influenza	0	1	0	0
Intervertebral disc protrusion	0	1	0	0
Nephrolithiasis	0	1	0	0
Neuralgia	0	1	0	0
Pain	0	1	0	0

Pneumonia	1		0	0
Renal disorder	0	1	0	0
Staphylococcal bacteremia	0	1	0	0
Upper respiratory tract infection	0	1	0	0
Urethral obstruction	0	1	0	0
Anemia	0	0	0	1
Cardiac failure	0	0	0	1
Erysipelas	0	0	1	1
Hip fracture	0	0	0	1
Ileus	0	0	0	1
Esophageal achalasia	0	0	0	1
Pleural effusion	0	0	0	1
Subcutaneous emphysema	0	0	0	1

* See reviewer comment below
Source: PALOMA-1 CSR, modified Table 72, page 248

Reviewer Comment: *There was a higher percentage of patients in the palbociclib plus letrozole arm that had SAE compared with the letrozole alone arm. The higher rate of pulmonary embolism is concerning. The total number of patients experiencing pulmonary embolism was 4, however one patient was noted to have PE incidentally and was not thought to have had a serious event by the investigator as she was not hospitalized, remained on palbociclib and had no symptoms of PE (Subject ID 10332007).*

Patient 10913002 Case of Ischemic Colitis

A 55-year-old, Caucasian, female from Spain with no history of thromboembolism nor any cardiac disorder or concomitant medications was admitted to hospital on (b) (6) (b) (6) (started therapy February 7th, 2012) with lower gastrointestinal bleed due to ischemic colitis confirmed by a colonoscopy and biopsy. On admission, labs included: hemoglobin 12.1 g/dl and platelets 232 x10 3/mm3, leukocytes 7.4 x10 9/L.
Palbociclib was permanently discontinued on June 27th, 2012 and on July 17th, 2012; the subject was discontinued from the study but continued with letrozole out of the study. The subject recovered from the event ischemic colitis and was discharged. Diagnostic of the discharge report included lower gastrointestinal tract hemorrhage and ischemic colitis (mild-moderate).

Reviewer Comment: *Colitis with ischemia needs to be graded as grade 4 per CTCAEV3. Given there were additional 5 cases of PE with palbociclib present, there may be a potential causality for thromboembolic events with palbociclib.*

With the 120 day safety update (15 April 2014), a total of 19 patients (22.9%) in the palbociclib plus letrozole arm and 6 patients (7.8%) in the letrozole alone arm experienced at least 1 SAE in the Phase 2 part of the study. One additional patient of the palbociclib plus letrozole arm experienced any SAE as of 15 April 2014: 19 patients (22.9%) reported in the safety update versus 18 (21.7%) reported in the initial report for the total Phase 2 population. Four SAEs including Grade 3 campylobacter infection, Grade 2 gastritis, Grade 2 mastoiditis, and Grade 3 renal failure acute, which were not reported for the palbociclib plus letrozole arm as of 29 November 2013, were reported for that treatment arm as of April 15th, 2014. None of these four SAEs was assessed as related to treatment. Two new SAEs, plasma cell myeloma and upper limb fracture, were reported for the letrozole alone arm as of April 15th, 2014.

Study A5481001: *A Phase 1 Clinical, Pharmacokinetic, and Pharmacodynamic Evaluation of 2 Schedules of Oral PD 0332991, a Cyclin-Dependent Kinase Inhibitor, in Patients with Advanced Cancer*

Seven patients (9.5%) experienced a TEAE with a maximum severity of Grade 4 (. The Grade 4 TEAEs were neutropenia (4.1%) and anemia, thrombocytopenia, blood uric acid increased, hyperglycemia, and pulmonary embolism (1.4% each).

Ongoing Advanced Breast Cancer Phase 3 Study A5481008
As of the November 29th, 2013 data cut-off date, one patient (1/126 [0.8%]) experienced an event with a fatal outcome in ongoing Study A5481008; the event, cardiac arrest, was not considered related to the study drugs (blinded therapy and letrozole) by the investigator or the Applicant. The patient had a history of left axillary thrombophlebitis and pulmonary embolism was reported to be the suspected reason for the patient's death.

Reviewer Comment: *This is the only reported fatal case with pulmonary embolism. However, this study is blinded and it is not clear if the patient was on the palbociclib plus letrozole arm.*

7.3.3 Dropouts and/or Discontinuations

As of the November 29th, 2013 data cut-off date, 12 patients (14.5%) discontinued palbociclib plus letrozole due to an AE, and two patients (2.6%) discontinued letrozole due to an AE (Table 37).

With 120 day safety update (April 15th, 2014), there was one additional patient in the palbociclib plus letrozole arm of the Phase 2 Part 2 cohort who experienced treatment-related AEs of Grade 2 weight decreased and Grade 3 fatigue leading to permanent discontinuation from treatment.

Table 38: Treatment-Emergent Adverse Events Associated With Permanent Discontinuation by Preferred Term and (All Causalities) – Phase 2: As Treated Set

MedDRA Preferred Term	Palbociclib + Letrozole N=83		Letrozole N=77	
	Grade 1/2 N	Grade 3/4 N	Grade 1/2 N	Grade 3/4 N
Neutropenia	0	5	0	0
Colitis ischemic	0	1	0	0
Asthenia	1	0	0	0
Fatigue	0	1	0	0
Spinal pain	0	1	0	0
Fallopian tube cancer	0	1	0	0
Pulmonary embolism	0	1	0	0
Nausea	0	0	1	0
Arthralgia	0	0	0	1

Source CSR Page 253

7.3.4 Significant Adverse Events

The most common Grade 3/4 TEAEs observed following treatment with palbociclib plus letrozole were neutropenia, leukopenia, and anemia. The rate of Grade 3/4 neutropenia was 54.2% (48.2% Grade 3, 6% Grade 4) in the palbociclib plus letrozole arm, and the rate of Grade 3/4 neutropenia was 1.2% and 0% respectively in the letrozole alone arm.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Neutropenia

Neutropenia was the most frequently reported TEAE (Phase 1: 91.7%; Phase 2: 75.9% (49.4% with Grade 3 and 6% with Grade 4) in patients who received palbociclib plus letrozole in Study 1003. No cases of febrile neutropenia, neutropenic sepsis, or neutropenic infection were reported in Study A5481003. Seventy seven patients (93.9%) in the palbociclib plus letrozole arm of the Phase 2 part of Study A5481003 had abnormal absolute neutrophil counts, including 47 patients (57.3%) with Grade 3

abnormalities and 4 patients (4.9%) with Grade 4 abnormalities. Baseline characteristics were similar for all patients with and without neutropenia in the palbociclib plus letrozole arm.

There were 11 episodes of Grade 4 neutropenia in the Phase 2 portion of Study A5481003. Mean duration of Grade 4 neutropenia was between 6 and 10 days. Only in 1 case led to treatment discontinuation.

Most episodes of Grade 3 neutropenia (192/253) resolved by the patient's next assessment, three of the 192 episodes led to treatment discontinuation, and treatment was given for seven of the 192 episodes. The remaining 61 episodes of Grade 3 neutropenia had improved to Grade 1 or 2 by the next assessment, 1 of the 61 episodes led to treatment discontinuation and 1 of the 61 episodes led to treatment being given. Most (223/253 [88.1%]) episodes of Grade 3 neutropenia were treated by dose reduction or dose delay/temporary discontinuation. Mean duration of Grade 3 neutropenia was between 10 and 13 days.

Reviewer Comment: *Although neutropenia is very common on the palbociclib arm, it is reassuring that majority resolved within one to two weeks without complications.*

The association of neutropenia and infection is shown in Table 38.

Table 39: Association of Neutropenia and Infection- Phase 2

	Palbociclib + Letrozole N=83	**Letrozole N=77**
All Grade Neutropenia a, N	63	4
Overlapping with all grade Infections and Infestations b	23	0
Overlapping with grade 3 / 4 Infections and Infestations	1	0
Grade 3 / 4 Neutropenia, N	46	1
Overlapping with all grade Infections and Infestations	13	0
Overlapping with grade 3 / 4 Infections and Infestations	0	0

[a] Neutropenia includes preferred terms of neutropenia and neutrophil count decreased
[b] MedDRA SOC of Infections and Infestations
Source Summary of Clinical Safety, Page 149, modified Table 63

Reviewer comment: *The majority of patients in the palbociclib did not have concomitant events in the Infections and Infestations SOC. It is reassuring that only one patient with neutropenia had a concomitant Grade 3/4 event (Influenza) in this SOC.*

7.3.5.2 Infections

Phase 1 Part of Study A5481003
Six patients experienced TEAEs MedDRA system organ class (SOC) Infections and Infestations. None experienced a Grade 3/4 event. The most frequently reported TEAEs (>2 patients) within this SOC were Upper respiratory tract infection (3 patients) and Sinusitis (2). Influenza, Tooth infection, and Upper respiratory tract infection experienced by 1 patient each were considered to be related to treatment.

Phase 2 Part of Study A5481003
A higher rate of infections was observed in the palbociclib plus letrozole arm (55.4%) than in the letrozole alone arm (33.8%). There were no discontinuations from study treatment due to an infection-related event and no febrile neutropenia. Three patients (3.6%) had Grade 3 events (influenza, pneumonia, upper respiratory tract infection, and staphylococcal bacteremia), and one patient (1.2%) (Subject ID 10083003) had a Grade 4 event (gangrene) in the infections and infestations SOC.

Gangrene Case (Subject ID 10083003)
A 64 year old woman from Hungry with history of diabetes and hypertension started to receive palbociclib and letrozole on June 28th, 2011. Palbociclib and letrozole were stopped on July 1st, 2013 and July 8th, 2013 respectively due to progression of primary disease. On an unknown date in the beginning of (b) (6), the subject was found to have some infection on her left big toe. Gangrene on the left hallux and left leg phlegmone was identified. She was treated with antibiotics. On (b) (6) the subject was admitted to the hospital due to significant pain for 2 days, for which she could not sleep. Infectious and necrotic condition of the leg progressed therefore amputation of left big toe with gangrene and necrectomy of the left foot was done on the same day with urgency. The subject eventually expired on (b) (6) in the same course of hospitalization. The event of gangrene was considered by the investigator and applicant to be due to diabetes mellitus.

Reviewer Comment: *There is a possibility that palbociclib could have contributed to the development of gangrene. The event death had occurred outside of reporting period therefore the event was only considered Grade 4.*

Table 40: List of Infections seen on Phase 2 Part of Study A5481003

MedDRA Lowest Level Term	Palbociclib + Letrozole N=83	Letrozole N=77
Acute cystitis	0	1
Acute tonsillitis	0	1
Bronchitis	5	2
Catarrh	2	1
Chest infection	0	3
Cold	2	0
Cold symptoms	1	1
Common cold	9	9
Cystitis	3	0
Dental fistula	2	0
Diverticulitis	0	3
Ear infection	2	0
Gastric infection	1	0
Gastroenteritis	1	0
Head cold	3	1
Infection	1	1
Infection upper respiratory	1	0
Lower respiratory tract infection	1	0
Lung infection	1	0
Otitis	2	0
Pharyngitis	2	1
Pinkeye	1	0
Pneumonia	2	3
Recurrent urinary tract infection	1	0
Respiratory tract infection	0	1
Rhinitis	1	0
Sinus infection	0	1
Sinusitis	2	1
Skin infection	3	1
Tonsillitis	1	0
Tooth infection	2	0
Upper respiratory infection	5	2
Upper respiratory tract infection	4	0
Upper respiratory tract infection NOS	1	0
Urinary tract infection	7	4
Wound infection	1	0
Total	70	37

7.3.5.3 Eye disorders

A higher rate of eye disorders was observed in the palbociclib plus letrozole arm (20.5%) than in the letrozole alone arm (5.2%). There were no SAEs or Grade 3 or 4 TEAEs in the eye disorders SOC reported in either treatment arm (See Table 40).

Table 41: Treatment-Emergent Adverse Events In The System Organ Class of Eye Disorders (All Causalities) – Phase 2 A5481003

MedDRA Preferred Term	Palbociclib + Letrozole N=83	Letrozole N=77
Blindness	1	0
Cataract	1	0
Conjunctivitis	4	0
Diplopia	1	0
Dry eye	2	0
Eye irritation	3	0
Eye pruritus	1	0
Eye swelling	2	0
Lacrimation increased	2	0
Photophobia	3	1
Vision blurred	1	0
Visual acuity reduced	0	1
Visual impairment	0	1
Vitreous floaters	0	1
Total	17	4

Source CSR Page 264, modified Table 76

Reviewer Comment: *Numerically higher rate of eye disorders was seen in the palbociclib plus letrozole arm. Conjunctivitis is the most common AE followed by photophobia. A variety of eye events were seen in this open label study. However, the number of eye disorders was too few to draw conclusions.*

7.3.5.3 Pulmonary Embolism

A numerical increased rate of pulmonary embolism was observed in the palbociclib plus letrozole arm (4.8%) than in the letrozole alone arm (0%). In addition there was one case of pulmonary embolism seen in Phase 1 part of Study A5481003 (n=12). None of the cases were considered related to therapy by investigators. All cases were Grade 4 per CTCAE Grade. Summary of these five cases are shown in Table 41. The only type of arterial and venous thromboembolic adverse events that has been observed on the study is pulmonary embolism. There was one case of ischemic colitis that is not clear if it was embolic in nature.

Table 42: Summary of Cases With Pulmonary Embolisms reported from Study A5481003 as of 29 November 2013

PID	Age Country	Past Medical History Concomitant Meds	Time to Onset	Symptoms Hospitalized Outcome	Treatment Action Taken With Palbociclib
10312001	78F France	"no relevant medical history" Domperidone, tramadol, ceftriaxone, hydroxyzine	32d	Fatigue and dyspnea Yes Recovered	Heparin (salbutamol, ipratropium, etc.) Palbociclib permanently discontinued
10562001	52F Germany	Asthma, HTN, depression, pain, constipation Pregabalin, amitriptyline, budesonide/ formoterol, escitalopram, lorazepam, oxycodone, movicol	56d	None reported Yes Recovered	not mentioned Palbociclib permanently discontinued due disease progression (not due to SAE)
Phase 1 10011002	70F US	None None	773d	None No (told to go to ER) Recovered	Enoxaparin No change in palbociclib dose
10482001	81F Hungary	None Trimetazidine, perindopril, terc-butilamin, bisoprolol, methylprednisolone, potassium chloride	168d	None Yes Recovered	Enoxaparin Palbociclib held for 16 days, then continued
10332007	55F* Ireland	Deep vein thrombosis, hypocalcemia, hip arthroplasty, fatigue, pain, nausea, bone metastases Zoledronic acid	791d	None No Recovered	Enoxaparin No change in palbociclib dose

*Case initially reported in 22 October 2012 as non-serious adverse event, later upgraded to Grade 4 by the company.

7.4 Supportive Safety Results

The most common (≥20%) TEAEs observed following treatment with palbociclib plus letrozole were neutropenia, leukopenia, fatigue, anemia, nausea, arthralgia, alopecia, diarrhea, and hot flush, and the most common (≥20%) TEAE observed following treatment with letrozole alone was fatigue.

7.4.1 Common Adverse Events

The most common (≥20%) TEAEs observed following treatment with palbociclib plus letrozole were neutropenia, leukopenia, fatigue, anemia, nausea, arthralgia, alopecia, diarrhea, and hot flush, and the most common (≥20%) TEAE observed following treatment with letrozole alone was fatigue.

7.4.2 Laboratory Findings

Per protocol, hematology and blood chemistry were obtained at baseline, Day 1 and 14 of the first two cycles and Day 1 of the cycles ≥3. Hematology included hemoglobin, WBC, neutrophils, lymphocytes, platelet count. Blood chemistry included BUN (or urea), creatinine, albumin, AST/ALT, total bilirubin, alkaline phosphatase, LDH, sodium, potassium, calcium, magnesium, phosphorous, uric acid.

7.4.3 Vital Signs

Per protocol, only blood pressure and pulse rate were captured in CRF (on screening, and Day 1 of each cycle). These were obtained at screening and during each follow up visit. However, changes in vital signs thought to be abnormal (by the investigator) were reported as AEs and graded as per NCI CTCAE v.3.0.

No patients had SAEs reporting events consistent with clinically relevant changes in blood pressure, pulse rate, respiratory rate, or body temperature during the Phase 1/2 study and no clinically meaningful changes were observed in the treatment arm as compared to the control arm.

In Phase 2 (Ph2P1+Ph2P2), a higher percentage of patients in the palbociclib plus letrozole arm (30 patients, 36.1%) had a systolic BP value of >150 mmHg or a diastolic BP of >100 mmHg than in the letrozole alone arm (19 patients, 24.7%). An additional patient in the palbociclib plus letrozole arm had a systolic BP value of >200 mmHg or diastolic BP of >110 mmHg.

A similar percentage of patients in each arm had a maximum increase from baseline in systolic BP ≥20 mmHg (19 patients [22.9%] and 23 patients [29.9%] in the palbociclib plus letrozole arm and the letrozole alone arm, respectively). Four patients (4.8%) and 5 patients (6.5%) in the palbociclib plus letrozole and the letrozole arm, respectively, had a maximum increase from baseline in systolic BP ≥40 mmHg. Another patient in the palbociclib plus letrozole arm had a maximum increase from baseline in systolic BP ≥60 mmHg.

7.4.4 Electrocardiograms (ECGs)

For full details, see Clinical Pharmacology review and QT-IRC review.

The QTc analysis was performed on the QTc Analysis Set, based on all treated patients with baseline and postbaseline data. All patients in Phase 1 and majority of patients in Phase 2 were analyzed for QTc (See Table 42).

Table 43: Analysis Populations for Patients in Phase 2

Analysis Set	Palbociclib + Letrozole	Letrozole
Intent-to-treat	84	81
As treated Analysis Population	83	77
QTc Evaluable	83	75

Descriptive statistics (including the mean and 95% CI) were provided for the absolute value and time-matched changes from baseline in QT interval, QT interval corrected for heart rate using cube-root Fridericia's conversion (QTcF), QT interval corrected for the heart rate using the square-root Bazett's formula (QTcB), and a study-specific correction (QTcS) and other ECG parameters (heart rate and RR-interval) as appropriate.

In Phase 1/2 no clinically significant effects on QTc interval were observed with palbociclib plus letrozole treatment , and no patients had a post-baseline absolute mean maximum QTcF or QTcS value of >500 msec.

In the Phase 2 portion of PALOMA-1, the majority of patients in each treatment arm had normal ECG parameters at baseline and the median baseline QTcF interval was similar between the 2 treatment arms.

The worst median on-study QTcF [or QTcS] observation was comparable between the two treatment arms (422.0 msec [430.7 msec] and 419.0 msec [426.0 msec] in the palbociclib plus letrozole arm and the letrozole alone arm, respectively). The baseline intervals and worst on-study intervals for QTcF and QTcS in both the Ph2P1 Cohort and Ph2P2 Cohort were similar to that observed in the Phase 2 (Ph2P1+Ph2P2) dataset.
In Phase 2 (Ph2P1+Ph2P2), the majority of patients in each treatment arm had a maximum increase in QTcB, QTcF and QTcS from baseline of <30 msec. When using QTcF, one patient in each treatment arm had a maximum QTc interval increase from baseline of ≥60 msec. When using QTcS, two patients in each treatment arm had a ≥60 msec QTc interval increase from baseline. The percentage of patients in each category of maximum QTcF or QTcS interval increase across the treatment arms in both the Part 1 Cohort and the Part 2 Cohort was similar to that observed in the Phase 2 (Part 1 and Part 2) dataset.

7.4.5 Special Safety Studies/Clinical Trials

For full details, see Clinical Pharmacology review.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See the Clinical Pharmacology Review

7.5.2 Time Dependency for Adverse Events

See the Clinical Pharmacology Review

7.5.3 Drug-Demographic Interactions

Age

The overall incidence of SAEs was higher in patients ≥65 years (29.7%) than in patients <65 years (15.2%) in the palbociclib plus letrozole arm. Discontinuations due to AEs were similar for patients <65 years (13.0%) and patients ≥65 years (16.2%) in the palbociclib plus letrozole arm. The most frequently reported (≥20%) TEAEs in patients <65 years were neutropenia, fatigue, anemia, nausea, diarrhea, vomiting, constipation, and thrombocytopenia. The most frequently reported (≥20%) TEAEs in patients ≥65 years were fatigue, nausea, neutropenia, dyspnea, anemia, constipation, diarrhea, flatulence, rash, and abdominal pain. (See Table 43).

Table 44: Summary of TEAEs, SAE and Discontinuations due to AEs by Age

	Palbociclib + Letrozole N=83		Letrozole N=77	
	<65 N=46	≥65 N=37	<65 N=40	≥65 N=37
Patients with AEs	46	37	33	37
Grade 3 or 4	37	27	4	12
SAE	7	11	1	4
Grade 3 or 4 TRAEs	29	25	0	0
D/C due to AEs	6	6	1	1
D/C due to TEAEs	4	2	1	1

Source: Summary of Clinical Safety, modified Table 95, page 205

Reviewer comment: *There were some differences in safety parameters based on age in Study A5481003, but these differences do not indicate that dosage adjustment is required.*

Race

The majority of patients in both the palbociclib plus letrozole arm (75/83 [90.4%]) and the letrozole alone arm (69/77) of the Phase 2 part of advanced breast cancer Study 1003 were White. In the palbociclib plus letrozole arm, only six patients were Asian, one patient was Black, and one patient was classified as "Other" race. In the letrozole alone arm, only three patients were Asian, one patient was Black, and four patients were classified as "Other" race.

Reviewer Comment: *Due to the small numbers of patient, it is difficult to draw meaningful conclusions regarding the effect of race on the safety of palbociclib.*

Gender

All patients in advanced breast cancer Study 1003 were female.

Geographic Region

The majority of the patients in the palbociclib plus letrozole (79.5%) and letrozole alone arms (70.1%) were treated in Europe. In addition, 16.9% of patients (14/83) in the palbociclib plus letrozole arm and 26.0% of patients (20/77) in the letrozole alone arm were treated in North America. The remaining patients (3 in each treatment group) were in other regions.

Reviewer comment: *Due to the small numbers of patient, it is difficult to draw meaningful conclusions regarding the effect of region on the safety of palbociclib.*

7.5.4 Drug-Disease Interactions

See the Clinical Pharmacology review.

7.5.5 Drug-Drug Interactions

For full details, see Clinical Pharmacology Review.

In nonclinical studies, palbociclib and its active lactam metabolite, PF-05089326, demonstrated little or no inhibition of cytochrome P450 (CYP) 1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 enzyme activities. However, palbociclib and its metabolite, PF-05089326, caused time-dependent inhibition of CYP3A-mediated

midazolam 1'-hydroxylase and testosterone 6β-hydroxylase activities and, therefore, may have the potential for PK DDI with drugs for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance.

Palbociclib did not cause induction of CYP1A2, CYP2B6, CYP2C8, or CYP3A4 messenger ribonucleic acid expression and/or enzyme activity in vitro in human hepatocytes at concentrations exceeding 50-fold of the palbociclib unbound steady-state plasma Cmax determined at therapeutic doses in humans; thus, the potential for palbociclib to induce these enzymes is considered to be low at clinically relevant concentrations.

The potential for palbociclib to inhibit the activities of selected uridine diphosphate glucuronosyltransferase (UGT) enzymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was also assessed, and the likelihood of DDI associated with inhibition of these Phase 2 enzymes at clinically relevant concentrations is considered low.
Inhibition of efflux transporters (p-glycoprotein [P-gp] and breast cancer resistant protein [BCRP]), hepatic uptake transporters (organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3), hepatic efflux transporter (bile salt export pump [BSEP]), and renal transporters (organic anion transporter [OAT] 1, OAT3, and organic cation transporter [OCT] 2) by palbociclib was assessed in vitro and was considered to be unlikely at clinically relevant palbociclib concentrations.

In vitro, palbociclib is metabolized mainly by CYP3A and sulfotransferase 2A1 enzymes. Drugs that are known to induce or inhibit the activities of these enzymes may alter the clearance and systemic exposure of palbociclib.

As an orally administered drug that exhibits pH-dependent solubility, co-administration with gastric acid-reducing agents could significantly reduce the solubility of palbociclib in stomach and impair its absorption as well as bioavailability due to elevated gastric pH.

Reviewer Comment: *Given palbociclib is metabolized mainly by CYP3, strong inducers and inhibitors of this enzyme should be avoided. In addition* (b) (4) *needs to be avoided. These are appropriately addressed in the proposed PI.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See Pharmacology/Toxicology Review.

7.6.2 Human Reproduction and Pregnancy Data

See Pharmacology/Toxicology Review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Five patients (4 patients in Study A5481003 and one patient in Study A5481004) have reported a palbociclib overdose as of April 15th, 2014 data (120 day safety update).

In Study A5481003, one patient (11053004) took 100 mg, vomited and then took another 100 mg, two patients (10011008 and 10553003) received 200 mg instead of 125 mg for 13 and 21 days, respectively, and one patient (10793003) received 250 mg instead of 125 mg for 18 days. Patient 10011008 experienced nausea, vomiting, and dizziness, but the events resolved and no clinically significant findings were reported. There were no associated AEs reported for Patients 11053004 and 10553003; Patient 10793003 permanently discontinued due to Grade 4 neutropenia associated with the overdose. The patient did not receive any treatment for the neutropenia, which was considered resolved on follow-up Day 11 (Study Day 29). While the neutropenia was ongoing, the patient experience a number of non-serious AEs, thrombocytopenia, diarrhea, nausea, vomiting, mucositis, dysgeusia, peripheral neuropathy, and epistaxis.

Patient 10334002 from Study A5481004 received 150 mg QD for 12 days instead of 75 mg; no relevant AEs and no SAEs were experienced during this period.

Drug Abuse

There are no data available on the potential for drug abuse or dependence with palbociclib.

Withdrawal and Rebound

A formal study has not been conducted by the applicant to investigate withdrawal.

7.7 Additional Submissions / Safety Issues

Hyperglycemia

Altered glucose metabolism was observed in rats in longer duration studies, and correlated with pancreatic islet cell vacuolation representing degenerative changes consistent with loss of pancreatic beta cells and corresponding to decreases in insulin

production. Effects on eyes (cataracts/lens degeneration), incisor teeth (ameloblast degeneration), kidney (vacuolation of tubular epithelial cells), and adipose tissue (atrophy) were considered secondary responses to the increased glycemia. Changes in glucose metabolism, the pancreas, and related secondary toxicities were not observed in dogs.

The pharmacology-toxicology review team sent an information request in order to evaluate whether there was a possible hyperglycemia signal in humans, measured glucose laboratory values (Study A5481001), reported adverse events (Study A5481001 and A5481003), and reported serious adverse events (across the Pfizer Safety database) were analyzed by the Applicant. These analyses did not indicate any apparent effect of duration of palbociclib exposure or of palbociclib dose on glucose levels (Study A5481001), nor was there an imbalance of the number of adverse event reports between the randomized treatment arms of Study A5481003. Only one serious adverse event of hyperglycemia was reported in a patient with pre-existing diabetes treated with dexamethasone in Study A5481004.

Even though the likelihood of hyperglycemia occurring in humans as a result of treatment with palbociclib appears to be low based on both the differences in pancreatic beta cell biology and the lack of an apparent signal in the available clinical database, The Applicant will monitor for and evaluate potential signals of hyperglycemia in ongoing and planned clinical studies using a variety of measures, including HbA1c, which best reflects chronic glucose elevations.

8 Postmarket Experience

Palbociclib is not marketed in the United States or other jurisdiction.

9 Appendices

9.1 Advisory Committee Meeting

No advisory committee meeting was held for this NDA.

9.2 Labeling Recommendations

There were extensive internal labeling discussions with all review disciplines and labeling negotiations are ongoing at the time of finalization of this review and have not been finalized. Key clinical labeling recommendations included:

- In order to prevent confusion, the indication was modified to: "IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease."
- In the Highlights Section and Indications and Usage Section 1, it was specified that the current approval is to be under accelerated approval provisions based on progression-free survival and that continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Specific dose modifications and management for neutropenia were included in Section 2.
- In Section 5 Warnings and Precautions, data was included for neutropenia, infections and pulmonary embolism.
- In Section 7, Drug Interactions, (b) (4) CYP3A inducers were described as medications to avoid.
- The results from PALOMA-1 (Study 1 in the label) was described in Section 14.
- Addition of the central radiography review assessment of PFS was added.
- (b) (4) were removed from the label (b) (4). Prescribers were not likely to know the difference between (b) (4). Please see the statistical review for additional information regarding (b) (4).

9.3 Literature Review/References

1. SEER Cancer Statistics Database.
2. Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes & development 1999;13:1501-12.
3. Rocca A, Farolfi A, Bravaccini S, Schirone A, Amadori D. Palbociclib (PD 0332991) : targeting the cell cycle machinery in breast cancer. Expert opinion on pharmacotherapy 2014;15:407-20.
4. Gillett C, Fantl V, Smith R, et al. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining. Cancer research 1994;54:1812-7.
5. Arnold A, Papanikolaou A. Cyclin D1 in breast cancer pathogenesis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:4215-24.
6. Santarius T, Shipley J, Brewer D, Stratton MR, Cooper CS. A census of amplified and overexpressed human cancer genes. Nature reviews Cancer 2010;10:59-64.
7. Cancer Genome Atlas N. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61-70.
8. Catalog of Somatic Mutations in Cancer (COSMIC) v71. (Accessed 12/9/2014, at http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/.)
9. Knudsen ES, Knudsen KE. Tailoring to RB: tumour suppressor status and therapeutic response. Nature reviews Cancer 2008;8:714-24.

10. Musgrove EA, Caldon CE, Barraclough J, Stone A, Sutherland RL. Cyclin D as a therapeutic target in cancer. Nature reviews Cancer 2011;11:558-72.
11. Elsheikh S, Green AR, Aleskandarany MA, et al. CCND1 amplification and cyclin D1 expression in breast cancer and their relation with proteomic subgroups and patient outcome. Breast cancer research and treatment 2008;109:325-35.
12. Kenny FS, Hui R, Musgrove EA, et al. Overexpression of cyclin D1 messenger RNA predicts for poor prognosis in estrogen receptor-positive breast cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 1999;5:2069-76.
13. Ahnstrom M, Nordenskjold B, Rutqvist LE, Skoog L, Stal O. Role of cyclin D1 in ErbB2-positive breast cancer and tamoxifen resistance. Breast cancer research and treatment 2005;91:145-51.
14. Rudas M, Lehnert M, Huynh A, et al. Cyclin D1 expression in breast cancer patients receiving adjuvant tamoxifen-based therapy. Clinical cancer research : an official journal of the American Association for Cancer Research 2008;14:1767-74.
15. Stendahl M, Kronblad A, Ryden L, Emdin S, Bengtsson NO, Landberg G. Cyclin D1 overexpression is a negative predictive factor for tamoxifen response in postmenopausal breast cancer patients. British journal of cancer 2004;90:1942-8.
16. Han S, Park K, Bae BN, et al. Cyclin D1 expression and patient outcome after tamoxifen therapy in estrogen receptor positive metastatic breast cancer. Oncology reports 2003;10:141-4.
17. Muss HB, Bunn JY, Crocker A, et al. Cyclin D-1, interleukin-6, HER-2/neu, transforming growth factor receptor-II and prediction of relapse in women with early stage, hormone receptor-positive breast cancer treated with tamoxifen. The breast journal 2007;13:337-45.
18. Linke SP, Bremer TM, Herold CD, Sauter G, Diamond C. A multimarker model to predict outcome in tamoxifen-treated breast cancer patients. Clinical cancer research : an official journal of the American Association for Cancer Research 2006;12:1175-83.
19. Reis-Filho JS, Savage K, Lambros MB, et al. Cyclin D1 protein overexpression and CCND1 amplification in breast carcinomas: an immunohistochemical and chromogenic in situ hybridisation analysis. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2006;19:999-1009.
20. Fry DW, Harvey PJ, Keller PR, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Molecular cancer therapeutics 2004;3:1427-38.
21. Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast cancer research : BCR 2009;11:R77.
22. Dean JL, Thangavel C, McClendon AK, Reed CA, Knudsen ES. Therapeutic CDK4/6 inhibition in breast cancer: key mechanisms of response and failure. Oncogene 2010;29:4018-32.
23. (NCCN) NCCN. NCCN Clinical practice guidelines in oncology.
24. O'Brien KM, Cole SR, Tse CK, et al. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. Clinical cancer research : an official journal of the American Association for Cancer Research 2010;16:6100-10.

25. Bergh J, Jonsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:1919-25.
26. Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27:4530-5.
27. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. The New England journal of medicine 2012;367:435-44.
28. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. Journal of the National Cancer Institute 2000;92:205-16.
29. Wiedemeyer WR, Dunn IF, Quayle SN, et al. Pattern of retinoblastoma pathway inactivation dictates response to CDK4/6 inhibition in GBM. Proceedings of the National Academy of Sciences of the United States of America 2010;107:11501-6.

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/s/

JULIA A BEAVER
01/22/2015

PATRICIA CORTAZAR
01/22/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207103 **Applicant: Pfizer** **Stamp Date:** 8-13-14

Drug Name: Palbociclib **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				**505(b)(1)**
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:		X		
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: **Study1003, with two cohorts** **Indication:1st line ER+ metastatic breast cancer** Pivotal Study #2 Indication:	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Laleh Amiri-Kordestani and Julia Beaver	9/12/14
Reviewing Medical Officer	Date
Patricia Cortazar	9/12/14
Clinical Team Leader	Date

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/s/

LALEH AMIRI KORDESTANI
09/15/2014

PATRICIA CORTAZAR
09/15/2014