# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207103Orig1s000

# SUMMARY REVIEW

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | 2/3/2015 |
| **From** | Amna Ibrahim MD |
| **Subject** | Division Director Summary Review |
| **NDA/BLA #**<br>**Supplement #** | 207103<br>1 |
| **Applicant Name** | Pfizer Inc |
| **Date of Submission** | 8/13/2014 |
| **PDUFA Goal Date** | 4/13/2015 |
| **Proprietary Name /**<br>**Established (USAN) Name** | Ibrance<br>Palbociclib |
| **Dosage Forms / Strength** | Capsule/125 Mg |
| **Proposed Indication(s)** | 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. |
| **Action/Recommended Action for NME:** | Accelerated Approval |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Beaver, Julia A./ Amiri Kordestani, Laleh |
| Statistical Review | Bloomquist, Erik W. |
| Pharmacology Toxicology Review | Chen, Wei |
| CMC Review/OBP Review | Crich, Joyce Z./Hughes, Minerva/ Chen, Xiao H. |
| Clinical Pharmacology Review | Fourie Zirkelbach, Jeanne/ Zhao, Liang/ Charlab Orbach, Rosane |
| Microbiology Review | Jessica G Cole |
| DDMAC | Toscano, Marybeth |
| DSI | Iacono-Connors, Lauren |
| CDTL Review | Cortazar, Patricia |
| OSE/DMEPA | Mathew, Davis |
| DMPP/OPDP | Walker, Morgan |
| OSE/DRM | Patel, Mona |
| Maternal Health Team Consult | Ceresa, Carrie |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRM=Division of Risk Management
CDTL=Cross-Discipline Team Leader

# 1. Introduction

Pfizer Inc. submitted NDA 207103 for Ibrance (palbociclib) for the following proposed 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 who have not received previous systemic treatment for their advanced disease.*

The indication was amended as below

> *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*.
>
> *This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*

A breakthrough designation was granted on April 1, 2013 based on the results a Phase 1/2 trial (PALOMA-1) that appeared to demonstrate a substantial improvement in Progression-Free Survival (PFS) compared to existing therapy.

The results from this Phase 1/2 open-label, randomized study (PALOMA-1), evaluating palbociclib in combination with letrozole in post-menopausal women with advanced ER-positive, HER2-negative breast cancer form the basis of this NDA. In this study, patients were randomly allocated to receive either palbociclib in combination with letrozole or letrozole alone. The median investigator-assessed PFS was 20.2 months (95% CI 13.8, 27.5) in the palbociclib plus letrozole arm and 10.2 months (95% CI 5.7, 12.6) in the letrozole alone arm [HR 0.488 (95% CI 0.319, 0.748)]. The safety profile appears to be tolerable.

There were several issues that arose because this trial was not designed for submission for a marketing approval. These issues will be discussed in this review.

# 2. Background

Breast cancer is the most common cancer in women. While generally the mortality in breast cancer has been improving, there is a need for better treatments for breast cancer patients. In first-line treatment of women with ER-positive, HER2-negative breast cancer, an improvement of less than a year of PFS is generally achieved.

The basis of approval for letrozole in first-line treatment of hormone receptor-positive or

hormone receptor-unknown breast cancer is a randomized trial that compared letrozole (Femara) with tamoxifen in postmenopausal patients with locally advanced or metastatic breast cancer. In this trial, a 3.4 month advantage in median PFS (letrozole: 9.4 months vs tamoxifen: 6 months; HR 0.72) was demonstrated over tamoxifen. A substantial improvement in PFS and a favorable risk-benefit profile has been considered to confer clinical benefit in this setting.

Palbociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro treatment of ER-positive breast cancer cell lines with the combination of palbociclib and antiestrogens leads to increased cell senescence, which was sustained for up to 6 days following drug removal. In vivo studies using a patient-derived ER-positive breast cancer xenograft model demonstrated that the combination of palbociclib and letrozole increased the inhibition of Rb phosphorylation, downstream signaling and tumor growth compared to each drug alone.

A break-through designation was granted as mentioned above. Because the phase 2 trial was not designed to provide a basis for marketing approval, it presented several issues. Multiple preNDA meetings were held. At a preNDA meeting, top-line data was discussed and FDA expressed concern over data-driven amendments and difficulty in interpretation of the p-value and recommended that the applicant conduct an independent blinded review on all patients in the phase 2 of the trial. In another preNDA meeting, 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. Given the magnitude of benefit conferred, FDA agreed to review the data and results from PALOMA 1.

PALOMA-2 is the confirmatory trial for the indication under discussion. It is titled "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". The primary endpoint, enrollment criteria and stratification factors are similar to that of the PALOMA-1 trial. Accrual has completed to this trial and per the primary clinical review, an 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.

# 3. CMC/Device

The Biopharmaceutics review by Minerva Hughes, PhD, focused on relative bioavailability/bioequivalence studies for formulation changes (b) (4) which was reviewed by Clinical Pharmacology), dissolution method and acceptance criteria and the manufacturing process impact on dissolution. She recommended approval of the NDA. Joyce Crich PhD reviewed the drug product and Xiao Chen PhD reviewed the drug substance and recommend approval from CMC perspective. They stated that based on the provided stability data, a 24-month expiration dating period is granted for the drug product (75 mg, 100 mg, and 125 mg) when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF). The reviewers state that adequate data have

been provided for the manufacture and controls of the drug substance and drug product and that the microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective. The CMC revisions of the package insert were incorporated into the revised labeling for the labeling meeting of the NDA on 13-Jan-2015. The revised container labels, as amended by the applicant on 13-Jan-2015 are acceptable from the CMC perspective. The Office of Compliance issued an overall "acceptable" recommendation dated 30-Nov-2014 for all facilities used for manufacturing and control of the drug substance.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

## 4. Nonclinical Pharmacology/Toxicology

Wei Chen, PhD, recommends approval for this NDA. She states that the nonclinical studies adequately support the safety of oral palbociclib in 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. Additional nonclinical studies are not needed at this time. Per secondary review by Todd Palmby, PhD, "kinase inhibitor" was selected as the Established Pharmacologic Class for palbociclib. This is scientifically valid based on the submitted data and clinically meaningful, since adverse events observed in clinical trials were not unique to palbociclib and did not warrant a distinct pharmacologic class to alert prescribers to potential safety concerns that are not associated with other kinase inhibitors.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

## 5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review, dated 1/15/2015, states that "The Office of Clinical Pharmacology (Divisions of Clinical Pharmacology V and Pharmacometrics) have reviewed the information contained in NDA 20-7103. This NDA is considered acceptable from a clinical pharmacology perspective." According to the review, a definitive conclusion regarding an exposure-response relationship for PFS could not be made based on the limited data at a fixed dose of 125 mg from trial PALOMA-1. A greater reduction in absolute neutrophil count appears to be associated with increased palbociclib exposure. No clinically significant change in the QTc interval was detected when palbociclib was administered to steady state. Based on the human mass balance trial, palbociclib is primarily eliminated by hepatic metabolism. Based on the population pharmacokinetic analysis, a dose reduction is not needed in patients with mild or moderate renal impairment, or mild hepatic impairment. Palbociclib should be administered with food. One PMR (to evaluate the effect of hepatic impairment) and one PMC (drug interaction trial to study the effect of a CTP3A inducer on the PK of palbociclib) will be included in the action letter.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

# 6. Clinical Microbiology

Not applicable.

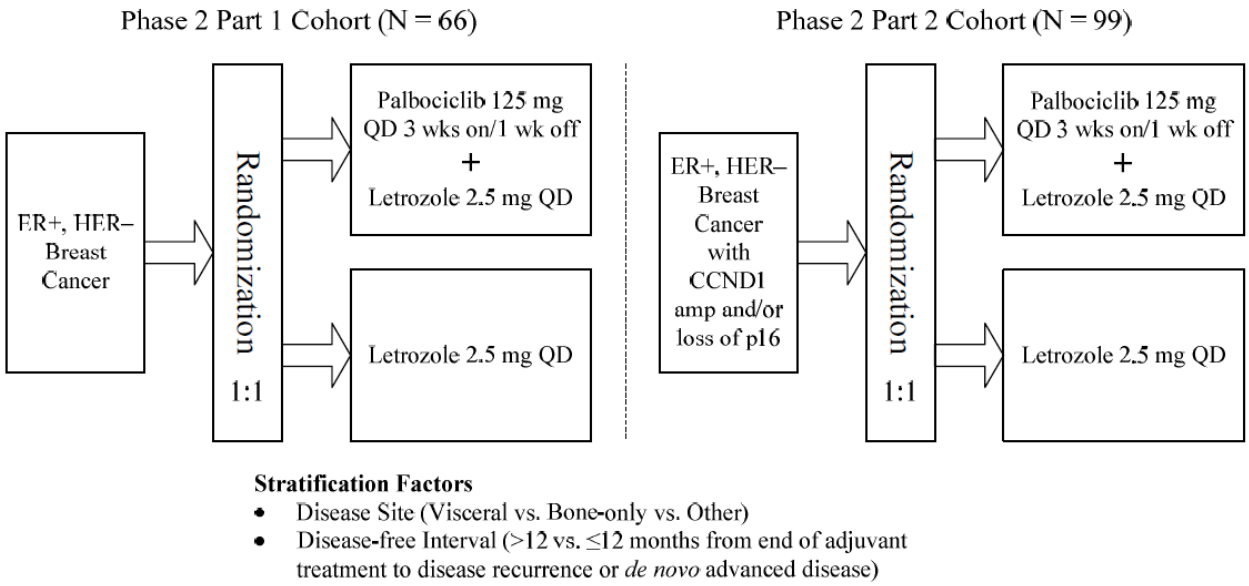
# 7. Clinical/Statistical-Efficacy

PALOMA-1 was a randomized, open-label, multicenter study of palbociclib plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. This study had a dose escalation, Phase 1 component (N=12) followed by the Phase 2 part. The phase 1 component will not be discussed further in this review.

The efficacy of palbociclib is based on the results of the Phase 2 portion of this study. There were several amendments made, including those that were data driven. The design of the study evolved over time. These changes include the following:

- Initially, the Phase 2 was to enroll 150 patients. However, based on the evolving preclinical data, in July 2010 (amendment 3), the Phase 2 was amended to include two parts; part 1 (approximate N=60) included an unselected population and part 2 (approximate N=150) that included patients with the biomarker-positive disease (tumors demonstrating CCND1 gene amplification and/or loss of the CDKN2A gene).

  **Figure: PALOMA 1 Phase 2 Study Overview**
  Applicant figure



- An interim analysis of part 1data showed clinical activity of palbociclib in combination with letrozole in both the biomarker-unselected and the biomarker-selected populations. After this interim analysis, enrollment in part 2 (biomarker-selected cohort) was terminated, at which time 99 patients had been accrued. In June 2012, the primary endpoint for the Phase 2 portion was changed from PFS from the part 2 cohort to PFS from both part 1 & 2 cohorts (amendment 5).

- In July 2013 (amendment 7), an adjustment was made for the final analysis plan for the primary endpoint of PFS. The final analysis of the primary endpoint of PFS was to be performed when approximately 95 PFS events had been accumulated.

The ITT analysis of the investigator assessment of PFS for part 1 and 2 combined was the primary analysis. Secondary analyses were the investigator assessment of PFS for part 1 and 2 separately, BICR assessment of PFS for part 1 and 2 combined and the BICR assessment of PFS for part 1 and 2 separately. Other secondary endpoints included overall survival (OS) and overall response rate (ORR).

Enrollment to Phase 2 is simplified by the applicant as follows:

| | | |
|---|---|---|
| Part1: Planned: 60 patients | Randomized: 66 patients | Treated: 62 patients |
| Part2: Planned: 150 patients | Randomized: 99 patients | Treated: 98 patients |

Efficacy Results of Phase 2 of PALOMA1:

A total of 165 patients were randomized to Phase 2. Approximately a fifth of the patients enrolled were from the US. Randomization was stratified by disease site (visceral versus bone only versus other) and by disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence versus ≤12 months from the end of adjuvant treatment to disease recurrence or de novo advanced disease). Palbociclib was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Patients received study treatment until progressive disease, unmanageable toxicity, or consent withdrawal.

Patients enrolled in this study had a median age of 63 years (range 38 to 89). The majority of patients were Caucasian (90%) and all patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Forty-three percent of patients had received chemotherapy and 33% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of advanced breast cancer. Forty-nine percent of patients had no prior systemic therapy in the neoadjuvant or adjuvant setting. The majority of patients (98%) had metastatic disease. Nineteen percent of patients had bone only disease and 48% of patients had visceral disease.

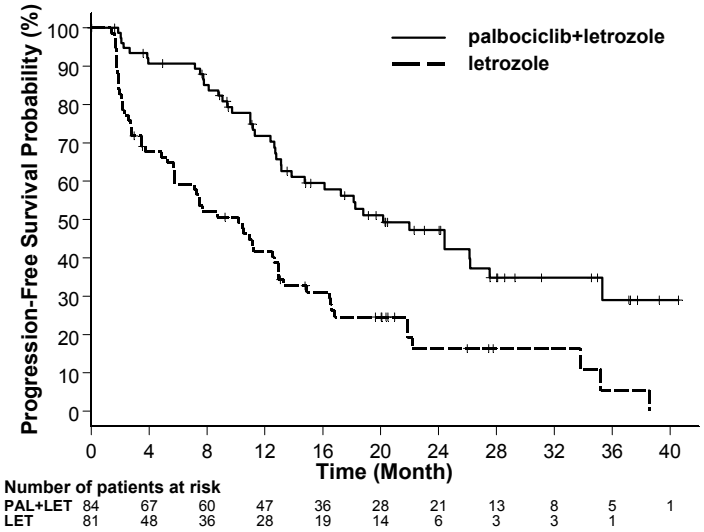
Investigator-assessed PFS is shown in table 1 and figure 1. The median PFS in the palbociclib plus letrozole arm was 20.2 months compared to 10.2 months in the letrozole alone arm, (HR=0.488, 95% CI: 0.319-0.748; nominal p>0.01). The treatment effect of the combination on PFS was also supported by a retrospective independent review of radiographs (see table 1). A 10-month difference in PFS was reported for the investigator and the BICR. Due to the number of data-driven changes to the SAP, (b) (4).

**Table 1: Efficacy Results – PALOMA 1 (Intent-to-Treat Population)**

| | Palbociclib + Letrozole (N=84) | Letrozole (N=81) |
|---|---|---|
| **Investigator –assessed PFS** | | |
| Number of PFS Events (%) | 41 (48.8%) | 59 (72.8%) |
| Hazard ratio (95% CI) | 0.488 (0.319, 0.748) | |
| Median PFS [months] (95% CI) | 20.2 (13.8, 27.5) | 10.2 (5.7, 12.6) |
| **BICR-assessed PFS** | | |
| Number of PFS Events (%) | 31 (36.9%) | 33 (40.7%) |
| Hazard ratio (95% CI) | 0.621 (0.378-1.019) | |
| Median PFS [months] (95% CI) | 25.7 (17.7-NR) | 14.8 (9.3-20.4) |

CI=confidence interval;
N=number of patients.
*Stratified by Part

**Figure 1: Kaplan-Meier Curves of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population)**



This study was not designed as a registration trial and there were several weaknesses in the study conduct. These include:

a) Data driven amendments to the statistical analysis plan.

   The study was not designed as a trial for marketing approval and multiple data driven amendments were made. On FDA's request, a blinded independent central review (BICR) was added. Multiple sensitivity analyses were performed and the palbociclib plus letrozole arm continued to show an improvement in benefit.

b) Incorrect stratification

   Per Dr Bloomquist, there were many misclassifications made for the stratification factors. These were balanced across the two arms. Although patients were stratified incorrectly, sensitivity analyses of PFS were performed using CRF data. These PFS analyses remained in favor of the palbociclib plus letrozole arm

c) Protocol deviations

   Protocol deviations were evaluated by the clinical team. Most deviations such as safety reporting and laboratory deviations would not affect the efficacy outcome. Where there were missed assessments, these were not followed by disease progression. In addition, most of the concomitant bisphosphonate treatment occurred on the control arm. The protocol deviations do not appear to be in favor of the palbociclib-containing arm.

d) Unequal censoring and discrepancy between BICR analysis and the investigator assessment for part 1

   PFS as assessed by investigator and by BICR is shown below. Both show a 10-month improvement in PFS. However, there appears to be a preferential bias in the investigator assessment censoring in part 1. More patients were censored on the investigational arm in the investigator-assessed analysis. FDA clinical and statistical teams looked at this in great detail. Most of the discrepancies from censoring were due to progressive disease, mainly in the bone on the investigational arm. 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. In addition, a stratified log-rank sensitivity analysis showed no difference in the overall conclusions. However, a bias favoring the palbociclib arm cannot be ruled out.

**Table 2: Investigator-assessed PFS by Part**

| | Part 1 (biomarker unselected) N=66 | | Part 2 (biomarker selected) N=99 | |
|---|---|---|---|---|
| | **Palbociclib + Letrozole N=34** | **Letrozole N=32** | **Palbociclib + Letrozole 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 (11.2-NR) | 5.7 (2.6-10.5) | 18.1 (13.1-27.5) | 11.1 (7.1-16.4) |
| **Hazard Ratio 95% CI p- value*** | 0.299 (0.156-0.572) <0.01 | | 0.508 (0.303-0.853) 0.0046 | |

*nominal p value
Table based on FDA statistics review

**Table 3: BICR-assessed PFS by Part**

| | Part 1(biomarker unselected) N=66 | | Part 2 (biomarker selected) N=99 | |
|---|---|---|---|---|
| | **Palbociclib + Letrozole N=34** | **Letrozole N=32** | **Palbociclib + Letrozole 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 (7.5-8.6) | 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 | |

*nominal p value
Table based on FDA statistics review

e) Underperforming control arm in part 1of investigator analysis
The difference in the median PFS in part 1 (20 months) is greater than in part 2 (7 months) of the investigator analysis of the study. This appears to be due to an underperforming control arm in part 1. As per Dr Beaver, based on historical information with recent aromatase trials in the first-line advanced breast cancer setting demonstrate a 10.2 to 13.5 month PFS. Larger number of patients with 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.

**Overall Survival:**
The OS results were not mature with only 37% being reported. The hazard ratio of 0.813 for the combined analysis was in favor of the palbociclib-containing arm.

**Table 4: Overall Survival**

| | Part 1 N=66 | | Part 2 N=99 | | Part 1 and Part 2 N=165 | |
|---|---|---|---|---|---|---|
| | P +L N=34 | L N=32 | P +L N=50 | L N=49 | P +L N=84 | L N=81 |
| **Events, n (%)** | 16 (47.1) | 15 (46.9) | 14 (28.0) | 16 (32.7) | 30 (35.7) | 31 (38.3) |
| **Median OS 95% CI** | 37.5 (27.6, NR) | 33.3 (26.0, NR) | NR (26, NR) | N (23.4, NR) | 37.5 (28.4, NR) | 33.3 (26.4, NR) |
| **HR 95% CI p- value*** | 0.844 (0.417-1.710) 0.3189 | | 0.783 (0.382-1.606) 0.2520 | | 0.813 (0.492-1.345) 0.2105 | |

*nominal p value
Table based on FDA statistics review

**Figure: Kaplan Meier Analysis of Overall Survival**

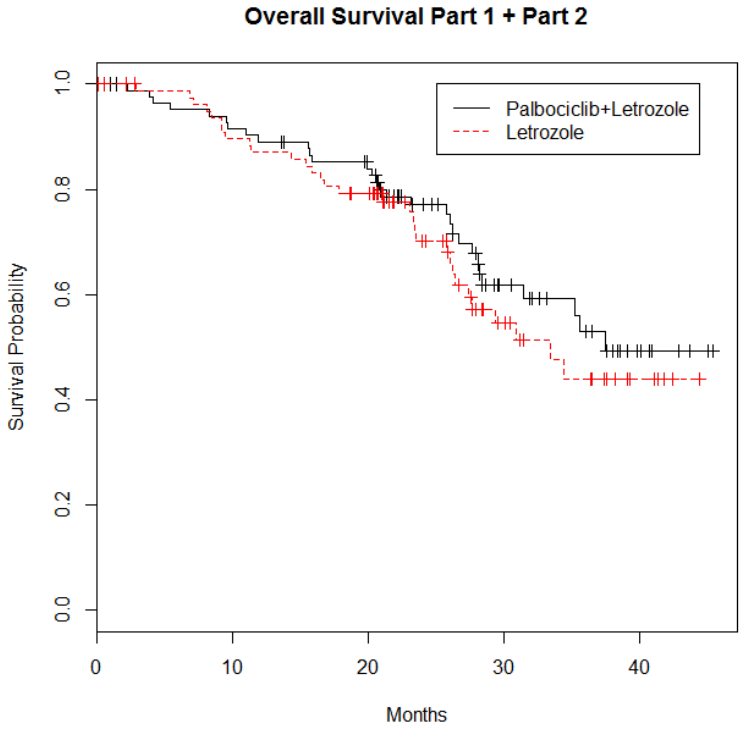
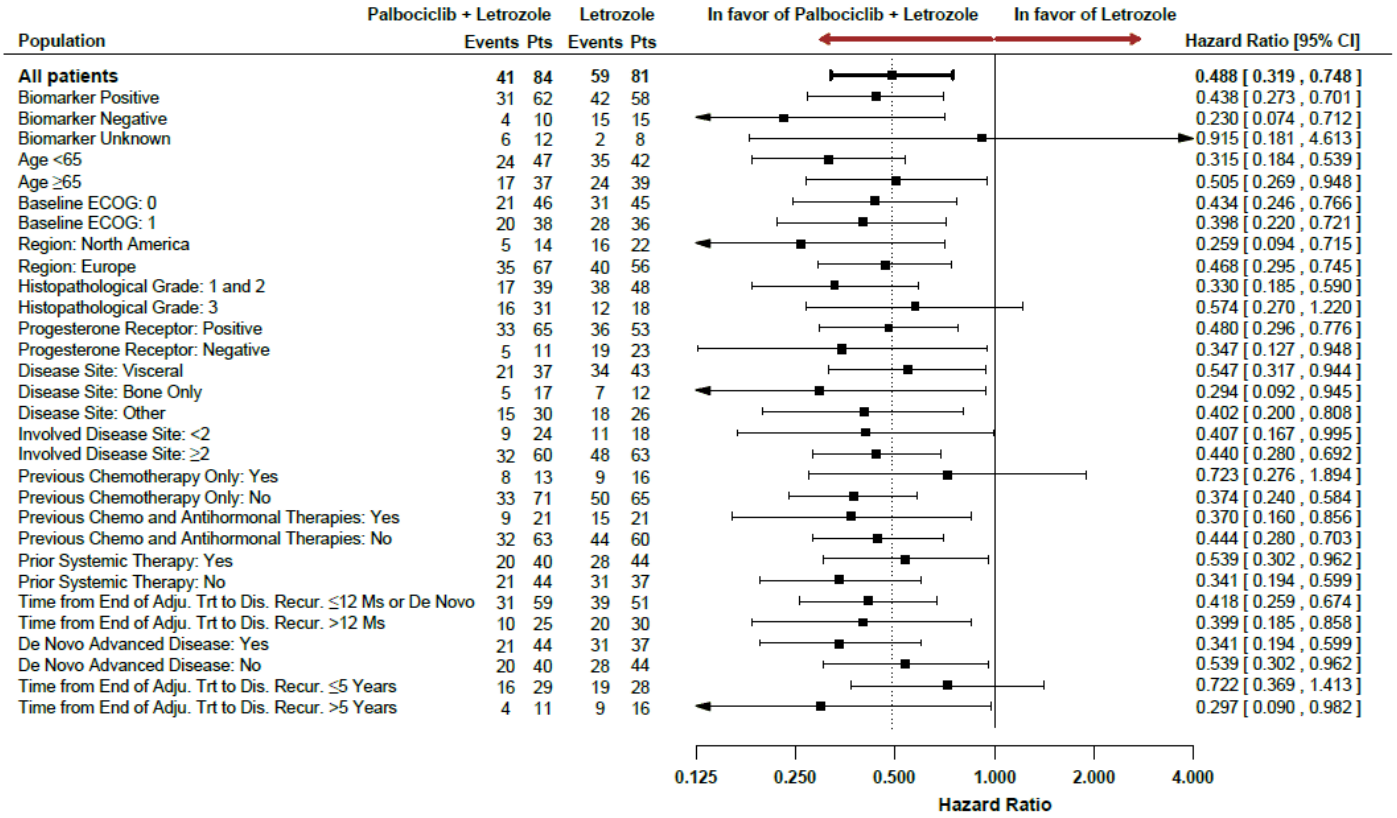



Figure from FDA statistics review

**Overall Response Rate:**
Overall response rate in patients with measurable disease as assessed by the investigator was higher in the palbociclib plus letrozole compared to the letrozole alone arm (55.4% versus 39.4%).

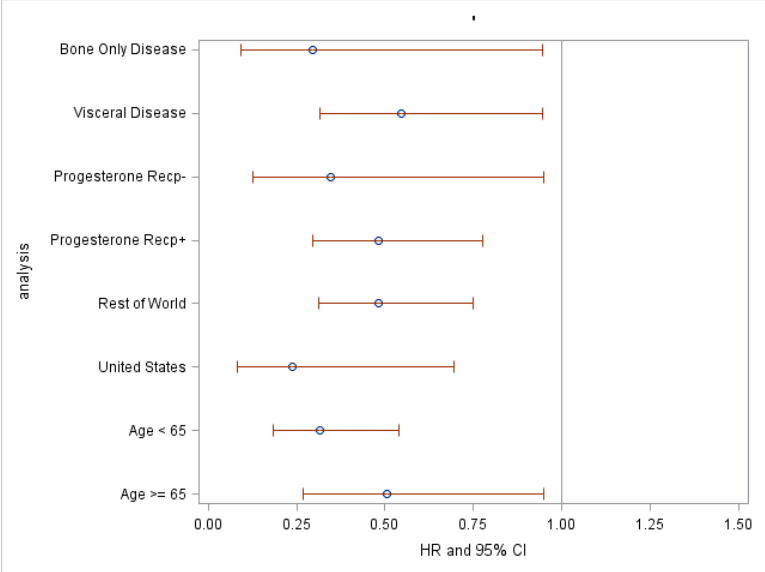
**Subgroup Analyses:**
Multiple subgroup analyses were performed by the applicant and by FDA. These were in favor of the palbociclib-containing arm as below.

**Figure: Primary and Subgroup Analyses of Investigator-Assessed PFS with Stratification Factors per CRF: ITT 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

**Figure: Investigator Assessed PFS Subgroup Analysis**
As per FDA reviewer




**Biomarker analysis:**
Regarding the biomarker analysis, Dr Beaver states that the results 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. However resistance to palbociclib was seen in another study in six out of nine glioblastoma cell lines with CDKN2A deletion. 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 warranted and the clinical post marketing commitment is meant to address the better detection of a predictive biomarker.

# 8. Safety

As reviewed by Dr. Amiri-Kordestani, the applicant submitted safety data for 755 patients/subjects. This included 297 healthy subjects and 458 patients with malignant disease. The clinical safety data supporting this NDA is primarily derived from PALOMA-1 (Phase 1, N=12, Phase 2, N=83). The median duration of treatment for palbociclib was 13.8 months while the median duration of treatment for letrozole on the letrozole monotherapy arm was 7.6 months.

Most common adverse reactions (greater than or equal to 10%) were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and

epistaxis. The most frequently reported serious adverse reactions in patients receiving palbociclib plus letrozole were pulmonary embolism (3 of 83; 4%) and diarrhea (2 of 83; 2%).

An increase incidence of infections events was observed in the palbociclib plus letrozole arm (55%) compared to the letrozole alone arm (34%). Grade 3 or 4 infections occurred in 5% of patients treated with IBRANCE plus letrozole whereas no patients treated with letrozole alone experienced a Grade 3 or 4 infection. Dr. Amiri-Kordestani, however, notes in her review that that only one patient with grade 3/4 neutropenia had a concomitant Grade 3/4 event (Influenza). Febrile neutropenia events have been reported in the palbociclib clinical program, although no cases were observed in PALOMA 1. Median time to first episode of any grade neutropenia per laboratory data was 15 days (13-117 days). Median duration of Grade ≥3 neutropenia was 7 days. Grade ≥3 neutropenia was managed by dose reductions and/or dose delay or temporary discontinuation consistent with a permanent discontinuation rate of 6% due to neutropenia.

Neutropenia, infections and pulmonary embolism were included in the Warning and Precautions section of the label.

Permanent discontinuation due to an adverse reaction occurred in 7 of 83 (8%) patients receiving IBRANCE plus letrozole and in 2 of 77 (3%) patients receiving letrozole alone. Adverse reactions leading to discontinuation for those patients receiving IBRANCE plus letrozole included neutropenia (6%), asthenia (1%), and fatigue (1%). The combination of palbociclib and letrozole appears to have an acceptable toxicity profile.

## 9. Advisory Committee Meeting

The NDA was not presented for discussion at an Advisory Committee meeting because outside expertise was not necessary. There were no controversial issues that would benefit from advisory committee discussion.

## 10. Pediatrics

Breast cancer does not exist in pediatric patients and is on the list of diseases for which a waiver from conducting pediatric studies is granted. The request for a waiver in pediatric patients will be discussed at PeRC.

## 11. Other Relevant Regulatory Issues

- DSI Audits: Four clinical sites were chosen for inspection based on number of enrolled patients. Three of these sites were foreign. The applicant and CRO who performed the BICR were also inspected. One of the study sites that enrolled 20 patients was found to be inadequate. The inspection revealed protocol deviations, GCP compliance deficiencies and underreporting of adverse events. The primary efficacy endpoints were verified.

A preliminary assessment of impact on site data exclusion was conducted by the DOP1 clinical and statistical reviewers. According to the OSI review, it was confirmed that none of the Form FDA 483 inspectional observations put subjects at significant risk nor affected key study outcome measures. However, due to the totality of the inspectional observations, OSI recommended that the data generated at this site not be used. The applicant is aware of the sites poor performance and has taken steps to ensure these irregularities would not be repeated. The inspection summary stated that there was no evidence that suggested that the issues were systemic across the study and that the data submitted appears reliable, other than the single site already mentioned.

The deviations from this site were reviewed in detail by the clinical review team. It was determined that no patient was placed at significant risk and key study outcome measures were not affected. A sensitivity analysis was performed removing all the patients from this site. This analysis did not change the conclusions of the study.

- Financial Disclosure: Eight investigators listed in the study report had financial information to disclose. As assessed by the clinical and statistics review teams, 39 patients (23%) of the patients were enrolled by these investigators. In a sensitivity analysis which removed 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.

- DDMAC: A consult was requested. All suggestions were discussed at labeling meetings and were incorporated as appropriate.

There are no other unresolved relevant regulatory issues.

## 12. Labeling

The major change was that the indication statement was ammended from the one initially proposed to avoid confusion by the breast cancer medical community (see section 1: Introduction). In addition, in a teleconference, the sponsor requested (b) (4) (b) (4) . This request was denied All issues were resolved.

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
  An accelerated approval is recommended 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.*

*This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*

- Risk Benefit Assessment

A single study with two cohorts have been submitted to support the NDA for 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. The magnitude of improvement in PFS is relatively large. ORR and OS results are supportive, as are the BICR results. Multiple sensitivity analyses were performed and these remained in favor of palbociclib. However, multiple issues arose, and while the p value is uninterpretable, and the magnitude of improvement of PFS may decrease relatively, it is likely that palbociclib will confer an improvement of several months of PFS. In addition, the safety profile is acceptable. All reviewers have recommended approval from their discipline's perspective.

The complexities of the issues and results were discussed several times and in depth with the review teams and within the Office of Hematology and Oncology Products. The consideration was whether in a serious disease setting where addition of palbociclib to letrozole doubles the PFS, and has an acceptable toxicity profile, should the approval be deferred until PALOMA-2 results are available. Given the observed risk-benefit profile, ongoing confirmatory trial PALOMA-2, the seriousness of the disease, I recommend an accelerated approval of palbociclib.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No REMS were needed or recommended.

- Recommendation for other Postmarketing Requirements and Commitments

Two PMRs and 2 PMCs will be included in the action letter, as listed on the next page.

**Postmarketing Requirements**

PMR #1 to fulfil the subpart H requirement

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 trial completion.

| | |
|---|---|
| Trial Completion: | 12/2016 |
| Final PFS Report Submission: | 06/2017 |
| Final OS Report Submission: | 11/2020 |

PMR #2 to assess the risk in patients with hepatic impairment

Submit the final report for your clinical trial A5481013 entitled, "A phase 1, open-label, single dose, parallel-group study to evaluate the pharmacokinetics of palbociclib (PD-0332991) in subjects with impaired hepatic function," to assess the effect of moderate and severe hepatic impairment on the pharmacokinetics of palbociclib.

| | |
|---|---|
| Trial Completion: | 06/2017 |
| Final Report Submission: | 12/2017 |

**Postmarketing Commitments**

PMC #1 – to conduct a drug interaction trial to study the effect of a CTP3A inducer on the PK of palbociclib

Submit the final report for your ongoing drug interaction trial (A5481039) entitled, "A phase 1, open-label, fixed-sequence, 2-cohort, 2-period study to investigate the effect of modafinil and pioglitazone given as multiple doses on single dose pharmacokinetics of palbociclib (PD-0332991) in healthy volunteers", to assess the effect of modafinil (a moderate CYP3A inducer) on the pharmacokinetics of palbociclib in healthy volunteers.

| | |
|---|---|
| Trial Completion: | 04/2015 |
| Final Report Submission: | 10/2015 |

PMC #2- to study the prognostic/predictive significance of the genetic alteration to the safety and efficacy of palbociclib

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.

| | |
|---|---|
| Trial Completion: | 12/2016 |
| Final Report Submission: | 06/2017 |

Amna Ibrahim MD
Acting Division Director
DOP1, OHOP

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

AMNA IBRAHIM
02/03/2015