

Name: Lynn McRoy MD FACS  
Company/Organization: Pfizer Inc. Oncology Business Unit  
Address: 235 East 42<sup>nd</sup> Street, MS 219-6, New York, New York 10017  
Phone: 212-733-4621  
Email: lynn.mcroy@pfizer.com  
Date of request: June 2, 2015  
NCCN Guidelines Panel: Breast Cancer

On behalf of Pfizer Oncology, I respectfully request the NCCN Breast Cancer Guideline Panel to review the enclosed for consideration of inclusion of IBRANCE® (palbociclib) in combination with fulvestrant as a treatment option for women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer after progression on endocrine therapy in the NCCN Breast Cancer Guideline.

- **Request for NCCN Guidelines Panel to consider review of data for a specific indication:**
  - The PALOMA-3 trial studied IBRANCE (palbociclib) in combination with fulvestrant in women with HR-positive, HER2 negative metastatic breast cancer who had progressed on prior endocrine therapy. The data were published online June 1 2015 in the *New England Journal of Medicine*. The median progression-free survival (PFS) was 9.2 months (95% confidence interval [CI], 7.5–not estimable) for palbociclib-fulvestrant and 3.8 months (95% CI, 3.5–5.5) for placebo-fulvestrant (hazard ratio 0.42, 95% CI, 0.32–0.56, P<0.001).
- **Specific changes recommended within the NCCN Guidelines:**
  - For women with HR+, HER2- metastatic breast cancer, recommend that treatment with IBRANCE (palbociclib) in combination with fulvestrant be listed as a treatment option those who have failed prior endocrine therapy.
- **Statement of whether the submitted use is or is not FDA approved for that indication**
  - The submitted use has not yet been approved by the FDA.
- **Rationale for recommended change [**
  - The availability of referenced efficacy and safety results from the Phase 3 randomized PALOMA-3 clinical trial.
- **Citation of literature support and complete articles supporting recommended change (attached):**
  - Turner NC, Ro J, Andre F, et al Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer *New England Journal of Medicine* E-pub June 1, 2015, DOI: 10.1056/NEJMoa1505270

A Phase 3 double blind, randomized, controlled, multicenter trial was conducted to evaluate the safety and efficacy of palbociclib 125mg in combination with fulvestrant 500 mg IM versus placebo in combination with fulvestrant in treatment of patients with advanced HR+, HER2- breast cancer who had failed prior endocrine therapy for their disease.

The trial enrolled 521 patients, randomized at a ratio of 2:1 to receive palbociclib (125 mg per day orally for 3 weeks followed by 1 week off) and fulvestrant (500 mg intramuscularly given per standard of care every 14 days for the first 3 injections and then every 28 days) or matching placebo and fulvestrant, respectively. Pre- or perimenopausal patients received goserelin for the duration of study treatment, starting at least 4 weeks before randomization and continuing every 28 days.

The PALOMA-3 study met its primary endpoint of investigator assessed PFS in the intent to treat population and was stopped early in April 2015 due to efficacy based on an assessment by an independent Data Monitoring Committee (DMC). The median PFS was 9.2 months (95% CI, 7.5 to not estimable) on palbociclib-fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) on placebo-fulvestrant (hazard ratio, 0.42; 95% CI, 0.32 to 0.56; P<0.001)

At the interim analysis cutoff date (December 5, 2014), 195 patients had experienced disease progression or death (102 events from the 347 patients on the palbociclib-fulvestrant arm and 93 from the 174 patients on the placebo-fulvestrant arm). 240 (69%) patients remain on treatment with palbociclib-fulvestrant and 75 (43%) on placebo-fulvestrant. The median relative dose intensity was 91.7% for palbociclib and 100% for fulvestrant in the palbociclib-fulvestrant groups, and 100% for both placebo and fulvestrant in the placebo-fulvestrant groups. Palbociclib dose was reduced in 109 (31.6%) patients versus 3 (1.7%) for placebo. The main reason for study treatment discontinuation was disease progression, occurring in 85 (25%) patients on palbociclib-fulvestrant and 87 (50%) on placebo-fulvestrant. Discontinuation of palbociclib or matching placebo therapy due to adverse events occurred in 7 (2%) patients on palbociclib, and 3 (1.7%) on placebo.

The adverse events observed with palbociclib in combination with fulvestrant in PALOMA-3 were consistent with their respective known adverse event profiles. The most common adverse events reported for the palbociclib-fulvestrant group were neutropenia, leukopenia, fatigue, and nausea. Febrile neutropenia and severe adverse events were similar in both arms in the study

Serious adverse events (any cause) occurred in 9.6% of patients in the palbociclib-fulvestrant group and 14.0% in the placebo-fulvestrant group. There were no serious adverse events that occurred in more than 1% of patients on palbociclib.

We appreciate the Panel's thorough consideration of Pfizer's recommendation that IBRANCE (palbociclib) in combination with fulvestrant be added to the treatment options for women with HR+, HER2- advanced breast cancer after progression on endocrine therapy.

Kind regards,

Lynn L. McRoy, MD FACS  
Senior Medical Director  
Pfizer Oncology  
235 East 42<sup>nd</sup> Street  
New York, NY 10017  
[lynn.mrcroy@pfizer.com](mailto:lynn.mrcroy@pfizer.com)



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