Palbociclib Combined With Fulvestrant in Premenopausal Women With Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results

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ABSTRACT

Background

The efficacy and safety of palbociclib, a cyclin-dependent kinase 4/6 inhibitor, combined with fulvestrant and goserelin was assessed in premenopausal women with advanced breast cancer (ABC) who had progressed on prior endocrine therapy (ET).

Patients and Methods

108 premenopausal endocrine-refractory women ≥18 years with HR+/HER2− ABC were among 521 women randomized 2:1 (347:174) to fulvestrant (500 mg) ± goserelin with either palbociclib (125 mg/d orally, 3 weeks on, 1 week off) or placebo. This analysis assessed whether the overall tolerable safety profile and significant progression-free survival (PFS) improvement extended to premenopausal women. Potential drug-drug interactions (DDIs) and ovarian suppression with goserelin were assessed via plasma pharmacokinetics and biochemical analyses, respectively.

Results

Median PFS for premenopausal women in the palbociclib (n=72) vs placebo arm (n=36) was 9.5 vs 5.6 months, respectively (hazard ratio, 0.50, 95% CI: 0.29–0.87), and consistent with the significant PFS improvement in the same arms for postmenopausal women. Any grade and grade ≤3 neutropenia, leukopenia, and infections were among the most frequent adverse events reported in the palbociclib arm with concurrent goserelin administration. Hormone concentrations were similar between treatment arms and confirmed sustained ovarian suppression. Clinically relevant DDIs were not observed.

Conclusion

Palbociclib combined with fulvestrant and goserelin was an effective and well-tolerated treatment for premenopausal women with prior endocrine-resistant HR+/HER2– ABC. Inclusion of both premenopausal and postmenopausal women in pivotal combination ET trials facilitates access to novel drugs for young women and should be considered as a new standard for clinical trial design.

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Implications for Practice

PALOMA-3, the first registrational study to include premenopausal women in a trial investigating a CDK4/6 inhibitor combined with endocrine therapy, has the largest premenopausal cohort reported in an endocrine-resistant setting. In pretreated premenopausal women with HR+ ABC, palbociclib plus fulvestrant and goserelin (LHRH agonist) treatment almost doubled median PFS and significantly increased the objective response rate vs endocrine monotherapy, achieving results comparable to those reported for chemotherapy without apparently interfering with LHRH agonist-induced ovarian suppression. The significant PFS gain and tolerable safety profile, strongly supports use of this regimen in premenopausal women with endocrine-resistant disease who could possibly delay chemotherapy.

Learning Objectives

BEST PRACTICE	CURRENT PRACTICE	RESULTING GAPS	LEARNING OBJECTIVES
Premenopausal women with HR+ MBC should be offered ovarian suppression or ablation in combination with hormone therapy. For premenopausal patients whose disease progresses on prior endocrine therapy, and for whom subsequent hormone therapies are indicated for their MBC, ovarian suppression should be maintained during treatment. Measurements of estradiol and FSH at baseline, before a premenopausal patient initiates treatment with a LHRHa and aromatase inhibitor, has been recommended. **Sources:** Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. J Clin Oncol. 2016;34:3069-3103. Papakonstantinou A, Foukakis T, Rodriguez-Wallberg KA, et al. Is estradiol monitoring necessary in women recieving ovarian suppression for breast cancer. J Clin Oncol. 2016;34:1573-1579.	Before the PALOMA-3 study, trials of clinical importance to investigate the effects of endocrine-based therapies on advanced breast cancer have been designed to only permit the participation of postmenopausal women, or less commonly, women who reach menopause prematurely owing to treatment-related ovarian failure. **Source:** Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425-439.	Questions persist because clinically important data are lacking in the current era to demonstrate the effects of endocrine therapy on premenopausal women with ABC. Premenopausal women with heavily-pretreated HR+ ABC and prior disease progression because of endocrine resistance require additional targeted treatment options that can extend the duration of an effective endocrine-based therapy with a tolerable safety profile and delay the need for chemotherapy if a rapid response is not required. **Source:** Rugo HS, Rumble RB, Macrae E, et al. J Clin Oncol. 2016;34: 3069-3103. Reinert T, Barrios CH. Optimal managment of hormone receptor positive metastatic breast cancer in 2016. Ther Adv Med Oncol. 2016 ;7:304-320.	Explain why palbociclib in combination with endorcine therapy and ovarian suppression should be considered for premenopausal women with prior endocrine-resistant HR+ ABC. Discuss the risk-benefit profile of treating premenopausal women with prior endocrine-resistant HR+ ABC with palbociclib plus fulvestrant and a LHRHa. Describe why the addition of palbociclib does not affect the ovarian suppression provided by LHRHa.

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ABC, advanced breast cancer; HR+, hormone receptor–positive; LHRHa, luteinizing hormone–releasing hormone agonist, MBC, metastatic breast cancer.

INTRODUCTION

Many women presenting with early breast cancer (BC) are premenopausal; upon relapse with advanced BC (ABC) most are postmenopausal, predominantly as a result of cytotoxic therapy and extended endocrine therapy (ET) treatment,[1] or via natural changes. Although younger women represent a low percentage of the patients diagnosed with breast cancer (20−34 years, 1.8%; 35−44 years, 8.9%),[2] presentation of early stage cancer at ≤40 years is prognostic in luminal breast cancer with the risk for relapse.[3,4] Survival outcomes are also worse for women <40 years than older age groups, notwithstanding intense treatment regimens.[3]

De novo metastatic and relapsed breast cancer can also occur in peri/premenopausal women (hereafter referred to as premenopausal women).[5,6] Yet premenopausal women have generally been excluded from large registrational trials involving hormonal agents to asses hormone-positive ABC; clinical data for premenopausal women remain remarkably limited to only a few small phase 2 trials.[7-9]

Endocrine resistance continues to pose serious clinical challenges.[10] Sequential ET is generally the preferred treatment for women with hormone receptor–positive (HR+) human epidermal growth factor receptor 2−negative (HER2–) metastatic BC.[11] Premenopausal women can benefit from ovarian suppression as part of their ET. Options include oophorectomy, radiotherapy[12], or medical suppression [13] with a luteinizing hormone–releasing hormone agonist. Although tamoxifen is used as the first-line ET for premenopausal women with HR+ BC (preferably with ovarian suppression[14]), aromatase inhibitors (AIs) plus luteinizing hormone–releasing hormone agonists can be more effective.[11,15] Fulvestrant, a pure estrogen receptor (ER) antagonist and selective ER degrader devoid of estrogenic effects[16] has not been standard

treatment for premenopausal women because of limited data supporting its biological effects.[17] In a neoadjuvant study of 66 premenopausal women with ER+ BC receiving 250 mg fulvestrant as monotherapy, fulvestrant did not significantly alter markers of hormone sensitivity (ER, progesterone receptor, and Ki67)[18] as it did in postmenopausal women.[19] Conversely, 750 mg fulvestrant did elicit significant changes in the same markers, similar to changes observed in premenopausal women treated with tamoxifen, suggesting a potential need for higher doses of fulvestrant in premenopausal women.[20]

When used in combination with ET, palbociclib, a selective inhibitor of cyclin-dependent kinases 4 and 6, resulted in a significant improvement in progression-free survival (PFS) compared with ET alone in both treatment-naive BC (PALOMA-1 trial: letrozole vs letrozole + palbociclib[21]; PALOMA-2 trial: letrozole + placebo vs letrozole + palbociclib[22]) and in women pretreated for HR+/HER2– ABC (PALOMA-3 trial: fulvestrant vs fulvestrant + palbociclib[6,23]).

In the randomized, phase 3 PALOMA-3 trial, palbociclib plus fulvestrant (± goserelin) prolonged investigator-assessed PFS compared with placebo plus fulvestrant (± goserelin) in women with HR+/HER2– ABC after prior progression on ET (median PFS 9.5 vs 4.6 months, respectively, hazard ratio, [HR] 0.46 [95% CI: 0.36–0.59], 2-sided log-rank $P<.0001$).[6] PALOMA-3 was the first registrational study to include premenopausal women in this setting; herein we describe the results by menopausal status, with a focus on premenopausal women with prior endocrine-resistant HR+/HER2– ABC.

PATIENTS AND METHODS

PALOMA-3 Study Design and Patients

The design of the PALOMA-3 phase 3, randomized, double-blind, placebo-controlled trial and definitions of the efficacy and safety parameters assessed have been described in detail elsewhere.[6,23] Key eligibility criteria include women ≥18 years with HR+/HER2− ABC whose disease had progressed on prior ET. One previous line of chemotherapy in advanced disease was allowed. Women were defined as premenopausal if they did not meet the criteria for postmenopausal status, defined as age ≥60 years, age <60 years and amenorrhea for ≥12 consecutive months (excluding an alternative pathologic or physiologic cause), and serum estradiol (E2) and follicle-stimulating hormone (FSH) concentrations within the laboratory reference range for postmenopausal women, documented bilateral oophorectomy, or medically confirmed ovarian failure.

Patients were randomized 2:1 to receive palbociclib (125 mg/d orally, 3 weeks on, 1 week off) plus fulvestrant (500 mg intramuscularly on day 1 and 15 of cycle 1 and once every 28-day cycle thereafter) or placebo plus fulvestrant. Premenopausal patients were required to receive a luteinizing hormone–releasing hormone agonist subcutaneously every 28 days starting ≥4 weeks before study treatment, and upon starting treatment any patients using an luteinizing hormone–releasing hormone agonist other than goserelin were switched to goserelin. Randomization was stratified by menopausal status, visceral metastases, and sensitivity to prior hormonal therapy.[6,23]

Biochemical assessments were performed on blood samples collected from premenopausal women on day 15 of study treatment. Plasma E2 analysis was conducted by InVentiv Health (Burlington, MA, USA) using gas chromatography (GC)/tandem mass spectrometry (MS-MS). The lower limit of quantification was 0.625 pg/mL. LH and FSH were measured at the Royal

Marsden Hospital by immunoradiometric assay (MG12151, IBL International, Hamburg, Germany; KIP0841, DIAsource, Ottignies-Louvain-la-Neuve, Belgium). The kit-reported detection limits were 0.2 and 0.1 mIU/mL, respectively.

Plasma pharmacokinetic (PK) samples were drawn predose on days 1 and 15 of cycles 1 and 2 and on day 1 of cycle 3 for the assessment of trough concentrations (C_{trough}) of palbociclib, fulvestrant, and goserelin (when applicable) in a subgroup of ~40 patients included in an initial interim safety assessment. Additional PK samples for plasma C_{trough} of palbociclib were drawn on day 15 of cycles 1 and 2 from all remaining patients.

Statistical Analysis

The Kaplan-Meier method[24] was applied to estimate median PFS (mPFS) and generate survival curves. A 2-sided unstratified log-rank test was used to compare treatment arms by menopausal status and a 1-sided unstratified log-rank test was used to compare treatment arms in subsets of premenopausal and postmenopausal patients ≤50 years as part of an exploratory analysis. The hazard ratio was estimated from the Cox proportional hazards regression model. Clinical benefit response (CBR) and objective response rate were evaluated and compared between treatment arms using a 1-sided exact test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomization. A multivariate analysis was run to evaluate the relationship between baseline prognostic factors with PFS. The final explanatory variables for the model were acquired using a backward selection process with a 0.1 significance level required for retaining the effects in the model. Descriptive analysis was used to summarize maximum-grade treatment-emergent adverse events (AEs). Biochemistry data were

summarized and *t* tests (one for each hormone) were used to compare data between treatment arms without a multiplicity adjustment for these or other exploratory analyses. The analyses for the potential for drug-drug interactions (DDIs) are described in detail in the appendix (supplementary text, online only). Statistical analyses were performed using SAS® Version 9.2 (SAS Institute, Cary, NC).

Before any study procedures were initiated, all patients provided written informed consent. Institutional review boards at participating centers approved all study-related procedures, which were conducted in accordance with the International Conference on Harmonisation, the guidelines for Good Clinical Practice, and the Declaration of Helsinki. Study enrollment is closed and the trial met its primary endpoint at interim analysis. The overall survival follow-up is in progress.

RESULTS

Between October 7, 2013, and August 26, 2014, 521 patients were randomly assigned to receive palbociclib plus fulvestrant (347 patients) or placebo plus fulvestrant (174 patients) with or without goserelin[6] (Appendix Fig. A1, online only).

Patient Demographics

A total of 108 (21%) women were premenopausal and 413 (79%) were postmenopausal. Overall, 42 (8%) women were ≤40 years, and 163 (31%) women were ≤50 years. Among premenopausal women, the mean age was 45 years; 83 (80%) of these patients were ≤50 years. Among postmenopausal women, 80 (19%) patients were aged ≤50 years. Demographic and baseline

characteristics are shown by menopausal status in **Table 1**. Half of the premenopausal women had received both tamoxifen and AI before enrollment. Baseline characteristics between treatment arms within menopausal subgroups were well balanced, except more premenopausal women had 2 prior lines of therapy in the ABC setting in the palbociclib than in the placebo arm (31.9% and 19.4%, respectively). Baseline characteristics between premenopausal and postmenopausal women were also well balanced, although the *ESR1* mutation rate by cfDNA was slightly lower in premenopausal women.

Efficacy

The data cutoff for this analysis was March 16, 2015, corresponding with the final primary efficacy analysis of PFS for the overall intent-to-treat population.[6] Investigator-assessed mPFS for palbociclib plus fulvestrant vs placebo plus fulvestrant in the premenopausal subgroup was 9.5 vs 5.6 months, respectively (hazard ratio, 0.50 [95% CI: 0.29–0.87], 2-sided *P*=.013). In the postmenopausal subgroup, mPFS was 9.9 vs 3.9 months (hazard ratio, 0.45 [0.34–0.59], 2-sided *P*<.0001). Kaplan-Meier survival curves for PFS are shown for premenopausal women in **Fig. 1**.[25]

In the palbociclib arm vs the placebo arm, investigator-assessed objective responses were observed in 25.0% (18/72) vs 11.1% (4/36) of premenopausal patients, respectively (odds ratio, 3.06 (95% CI: 0.82–13.38), *P*=.057; **Fig. 2**[26]). Significant improvement occurred with palbociclib plus fulvestrant vs placebo plus fulvestrant in investigator-assessed CBR, which was observed in 69.4% (50/72) vs 44.4% (16/36) of premenopausal women (OR 2.89 [95% CI: 1.15–7.34], *P*=.011).

Of those premenopausal women who underwent subsequent chemotherapy after disease progression, 58.6% (17/29) had received palbociclib plus fulvestrant whereas 78.3% (18/23) had received placebo plus fulvestrant. The median time to first chemotherapy treatment, relative to the date of randomization, was 120.0 (range, 37–354) days for women in the palbociclib arm and 74.5 (53–240) days for those in the placebo arm.

Exploratory Findings in Pre- and Postmenopausal Women ≤50 Years Old

Among premenopausal women aged ≤50 years (n=83), mPFS was 9.5 months in the palbociclib arm and 5.6 months in the placebo arm (hazard ratio, 0.53 [95% CI: 0.28–0.99], 1-sided unstratified log-rank test, *P*=.022; **Fig 1B**). Among postmenopausal women ≤50 years (n=80) in the palbociclib arm compared with the placebo arm, mPFS was 7.7 vs 4.5 months, respectively (hazard ratio, 0.49 [0.27–0.89], 1-sided unstratified log-rank test, *P*=.008; **Fig 1C**).

Prognostic Factors

Important and favorable prognostic factors in the final Cox proportional hazards multivariate model included absence of visceral disease for both premenopausal and postmenopausal patient subpopulations and Asian ethnicity for premenopausal patients. The treatment effect of palbociclib plus fulvestrant seen in the primary analysis of PFS held when the important prognostic factors were simultaneously adjusted in the multivariate analyses for both premenopausal and postmenopausal patients **(Table 2)**. When BMI was examined with the treatment arm in a separate multivariate model, lower values were more favorable for PFS.

Safety

Although all premenopausal women received goserelin concurrently with palbociclib plus fulvestrant, the safety profile was similar to that of postmenopausal women in terms of the type and frequency of AEs (all grades and grade 3–4), serious AEs (SAEs), the rate of dose reductions, cycle delays. Dose interruptions and discontinuation rate due to AEs were also similar for the palbociclib arm between menopausal subgroups (premenopausal, 5.6% and postmenopausal, 4.7%) **(Table 3)**.

Biochemical Analysis

After 15 days of study treatment, there was no significant difference in the mean concentrations of LH, FSH, or plasma E2 between those premenopausal patients receiving palbociclib or not; all unadjusted *P* values from the *t* tests were >0.05 **(Fig. 3)**. Mean E2 concentrations were consistent with those expected in the postmenopausal range. One patient in the palbociclib arm had an E2 value of 93.5 pg/mL, more than 3 times the upper limit of that group and not consistent with ovarian suppression. There was a statistically significant correlation between plasma E2 levels and body mass index (BMI) in both treatment arms (Spearman's rho = .44, *P*=.002 and .49, *P*=.02, respectively).

Drug-Drug Interaction Assessment

Results of the 1-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) analyses conducted to investigate the potential for DDIs among palbociclib, fulvestrant, and goserelin are shown in Appendix Table A1 (online only). The ratio of the adjusted geometric means (90% CI) for palbociclib from the final ANCOVA model and the within-patient mean steady-state concentration trough ($C_{troughSS}$) in the presence and absence of goserelin was 88.3%

(78.6%–99.1%). The ratio of the adjusted geometric means (90% CI) for goserelin within-patient mean $C_{troughSS}$ in the presence and absence of palbociclib was 110% (54.2%–225%). For the ratio of the adjusted geometric means (90% CI) for palbociclib from the final ANCOVA model, the within-patient mean $C_{troughSS}$ in the presence and absence of fulvestrant was 128% (117%–140%). The ratio of the adjusted geometric means (90% CI) for fulvestrant within-patient mean $C_{troughSS}$ in the presence and absence of palbociclib was 122% (101%–147%).

DISCUSSION

We report the results of the largest cohort of premenopausal women with prior endocrine-resistant HR+/HER2− ABC ever studied. The study found that premenopausal patients who received palbociclib plus fulvestrant significantly benefited compared with patients treated with placebo plus fulvestrant, consistent with the benefit observed for postmenopausal women. In premenopausal and postmenopausal women aged ≤50 years, PFS favored the palbociclib arm compared with the placebo arm, regardless of menopausal status and luteinizing hormone–releasing hormone agonist therapy.

Among all postmenopausal women, only 9 (2.2%) were ≤40 years and 71 (17.2%) were aged >40–50 years. The majority of these women possibly became postmenopausal as a result of previous chemotherapy for either primary or ABC, or ovarian suppression, a scenario more likely to occur in women >40 years whose ovarian function is inherently less resilient to such treatment.[27] Breast cancer incidence has been shown to peak in Asian women at a younger age compared with women from Western countries.[28] As expected, the proportion of Asian women

with ABC who were premenopausal (41% [44/108]) was at least 2-fold higher than for postmenopausal women (15% [61/413]) in this study.

Until recently, premenopausal women with HR+ metastatic BC who are candidates for ET were mainly treated with tamoxifen, with or without a luteinizing hormone–releasing hormone agonist. In a small study of 26 patients, median age 44 (range, 30–51) years, 250 mg fulvestrant (dose currently suboptimal) plus goserelin as first- to fourth-line therapy was reported to provide promising activity.[29] As an estrogen receptor downregulator, fulvestrant, unlike tamoxifen, is not efficacious in premenopausal women unless it is administered in combination with ovarian suppression.[30] In addition, a number of small phase 2 studies have shown the efficacy of AI treatment concurrent with luteinizing hormone–releasing hormone agonists.[7,8,31] The addition of a luteinizing hormone–releasing hormone agonist to tamoxifen or AIs has been shown to improve efficacy in early as well as ABC.[14,15,27,32,33] PALOMA-3 is the only phase 3 study to date to report outcomes data for fulvestrant 500 mg with ovarian suppression in premenopausal patients.[6] In premenopausal women in the control arm, mPFS with fulvestrant was 5.6 months. Accordingly, the fulvestrant label approved by the US Food and Drug Administration was recently expanded to include premenopausal women who receive concurrent ovarian suppression.[34]

Because of the low potential for a DDI between the protocol-specified concomitant medications and palbociclib based on their metabolic pathways and ability to affect the activity of relevant metabolic enzymes, this study was designed with the intention of confirming the lack of clinically significant DDIs using a sparse PK sample collection ($C_{troughSS}$ only) for each analyte. The magnitude of the ratios of the adjusted geometric means for the ANOVA and ANCOVA DDI analyses was not considered to represent a clinically meaningful difference.

The PK data confirms there were no clinically significant metabolic DDIs between palbociclib and goserelin or between palbociclib and fulvestrant when these 2 drugs were coadministered. Furthermore, the coadministration of goserelin did not have a clinically significant impact on fulvestrant plasma PK.

The clinical effectiveness of luteinizing hormone–releasing hormone agonists depends on their suppression of ovarian steroidogenesis. There is evidence that although these agents achieve complete cessation of ovarian E2 synthesis by the end of the first month of treatment, partial recovery can occur in some patients, apparently driven by progressive recovery of FSH levels.[35] Combining a luteinizing hormone–releasing hormone agonist with fulvestrant could still potentially result in incomplete ovarian suppression if E2 and FSH levels increase in response to fulvestrant.[35] We report hormonal concentrations measured after 15 days of fulvestrant treatment but after ≥6 weeks on goserelin, given goserelin was started 4 weeks before the study commenced. It is also important to note that the levels of E2 were measured with a highly sensitive GC/MS-MS, which avoids cross reactions with fulvestrant or its metabolites that can lead to highly aberrant values that more commonly occur using immunoassays.[36,37] Only one of 48 patients (2%) treated with palbociclib plus fulvestrant had an E2 value that was clearly premenopausal, but otherwise the values assessed for all patients were consistent with full ovarian function suppression, and there was no difference associated with the addition of palbociclib. This is supported by the significant relationship between plasma E2 levels and BMI; extragonadal estrogen production occurs mainly in subcutaneous fat[38] and resulting plasma concentrations are known to correlate with BMI.[39] Accordingly, there was no disruption of the correlation with the addition of palbociclib treatment. This underlines that the effect of palbociclib is independent of the background ET and supports the rationale for the concurrent

use of luteinizing hormone–releasing hormone agonists with ET in other studies currently recruiting participants.[40,41]

From a safety perspective, the incidence of any-grade and grade 3–4 AEs and SAEs was similar between premenopausal and postmenopausal women who received palbociclib plus fulvestrant, despite the addition of goserelin to the regimen. Dose modifications of palbociclib were also similar between premenopausal and postmenopausal groups.

Conclusions

The palbociclib plus fulvestrant regimen, with the addition of goserelin, essentially enables premenopausal women to be treated in close accordance with the guidelines for postmenopausal women, as recommended by the NCCN.[30] These findings show that the addition of palbociclib had no impact on the concentration of fulvestrant, complete ovarian suppression was maintained, and no additional toxicities were evident with the addition of a luteinizing hormone–releasing hormone agonist, all factors important for the investigation of palbociclib in early stage breast cancer. The results support the use of palbociclib in combination with fulvestrant and goserelin for women with HR+ ABC, and these findings have expanded the treatment options for premenopausal women.

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REFERENCES

1 Ganz PA, Land SR, Geyer CE, Jr. et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. J Clin Oncol 2011;29:1110-1116.

2 Howlander N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD.http://seer.cancer.gov/csr/1975_2013/, accessed September 1, 2016.

3 Gnerlich JL, Deshpande AD, Jeffe DB et al. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg 2009;208:341-347.

4 Partridge AH, Hiughes ME, Warner ET et al. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. J Clin Oncol 2016;34:1-8.

5 Dawood S, Broglio K, Ensor J et al. Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 2010;21:2169-2174.

6 Cristofanilli M, Turner NC, Bondarenko I et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425-439.

7 Wang J, Xu B, Yuan P et al. Phase II Trial of Goserelin and Exemestane Combination Therapy in Premenopausal Women With Locally Advanced or Metastatic Breast Cancer. Medicine (Baltimore) 2015;94:e1006.

8 Carlson RW, Theriault R, Schurman CM et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. J Clin Oncol 2010;28:3917-3921.

9 Park IH, Ro J, Lee KS et al. Phase II parallel group study showing comparable efficacy between premenopausal metastatic breast cancer patients treated with letrozole plus goserelin and postmenopausal patients treated with letrozole alone as first-line hormone therapy. J Clin Oncol 2010;28:2705-2711.

10 Murphy CG, Dickler MN. Endocrine resistance in hormone-responsive breast cancer: mechanisms and therapeutic strategies. Endocr Relat Cancer 2016;23:R337-352.

11 Cardoso F, Harbeck N, Fallowfield L et al. Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012 (suppl 7);23:vii11-19.

12 Hughes LL, Gray RJ, Solin LJ et al. Efficacy of radiotherapy for ovarian ablation: results of a breast intergroup study. Cancer 2004;101:969-972.

13 Rugo H, Rumble B, Macrae E et al. Endocrine therapy for hormone receptor–positive metastatic breast cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016;34:3069-3103.

14 Klijn JG, Beex LV, Mauriac L et al. Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. J Natl Cancer Inst 2000;92:903-911.

15 Pagani O, Regan MM, Walley BA et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014;371:107-118.

16 Wardell SE, Marks JR, McDonnell DP. The turnover of estrogen receptor alpha by the selective estrogen receptor degrader (SERD) fulvestrant is a saturable process that is not required for antagonist efficacy. Biochem Pharmacol 2011;82:122-130.

17 Ciruelos E, Pascual T, Arroyo Vozmediano ML et al. The therapeutic role of fulvestrant in the management of patients with hormone receptor-positive breast cancer. Breast 2014;23:201-208.

18 Robertson JFR, Semiglazov V, Nemsadze G et al. Effects of fulvestrant 250 mg in premenopausal women with oestrogen receptor-positive primary breast cancer. Eur J Cancer 2007;43:64-70.

19 Robertson JF, Nicholson RI, Bundred NJ et al. Comparison of the short-term biological effects of 7α-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5, (10)-triene-3,17B-diol(Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. Cancer Res 2001;61:6739-6746.

20 Young OE, Renshaw L, Macaskill EJ et al. Effects of fulvestrant 750mg in premenopausal women with oestrogen-receptor-positive primary breast cancer. Eur J Cancer 2008;44:391-399.

21 Finn RS, Crown JP, Lang I et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25-35.

22 Finn RS, Martin M, Rugo H et al. PALOMA-2: primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal

women with ER+/HER2– advanced breast cancer (ABC). Presented at: American Society of Clinical Oncology Annual Meeting; June 3–7, 2016; Chicago, IL.

23 Turner NC, Ro J, Andre F et al. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 2015;373:209-219.

24 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.

25 Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

26 Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-413.

27 Francis PA, Regan MM, Fleming GF et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015;372:436-446.

28 Leong SP, Shen ZZ, Liu TJ et al. Is breast cancer the same disease in Asian and Western countries? World J Surg 2010;34:2308-2324.

29 Bartsch R, Bago-Horvath Z, Berghoff A et al. Ovarian function suppression and fulvestrant as endocrine therapy in premenopausal women with metastatic breast cancer. Eur J Cancer 2012;48:1932-1938.

30 National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer. Version 1.2016. 2015. https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, accessed December 18, 2015.

31 Nishimura R, Anan K, Yamamoto Y et al. Efficacy of goserelin plus anastrozole in premenopausal women with advanced or recurrent breast cancer refractory to an LH-RH

analogue with tamoxifen: results of the JMTO BC08-01 phase II trial. Oncol Rep 2013;29:1707-1713.

32 Boccardo F, Rubagotti A, Perrotta A et al. Ovarian ablation versus goserelin with or without tamoxifen in pre-perimenopausal patients with advanced breast cancer: results of a multicentric Italian study. Ann Oncol 1994;5:337-342.

33 Klijn JG, Blamey RW, Boccardo F et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 2001;19:343-353.

34 FASLODEX® (fulvestrant). Full Prescribing Information, AstraZeneca Pharmaceuticals LP, Wilmington, DE, 2016.

35 Dowsett M, Lonning PE, Davidson NE. Incomplete estrogen suppression with gonadotropin-releasing hormone agonists may reduce clinical efficacy in premenopausal women with early breast cancer. J Clin Oncol 2016;34:1580-1583.

36 van Kruchten M, de Vries EG, Glaudemans AW et al. Measuring residual estrogen receptor availability during fulvestrant therapy in patients with metastatic breast cancer. Cancer Discov 2015;5:72-81.

37 Stanczyk FZ, Jurow J, Hsing AW. Limitations of direct immunoassays for measuring circulating estradiol levels in postmenopausal women and men in epidemiologic studies. Cancer Epidemiol Biomarkers Prev 2010;19:903-906.

38 Paatela H, Wang F, Vihma V et al. Steroid sulfatase activity in subcutaneous and visceral adipose tissue: a comparison between pre- and postmenopausal women. Eur J Endocrinol 2016;174:167-175.

39 Lønning PE, Haynes BP, Dowsett M. Relationship of body mass index with aromatisation and plasma and tissue oestrogen levels in postmenopausal breast cancer patients treated with aromatase inhibitors. Eur J Cancer 2014;50:1055-1064.

40 ClinicalTrials.gov. A study of palbociclib in addition to standard endocrine treatment in hormone receptor positive Her2 normal patients with residual disease after neoadjuvant chemotherapy and surgery (PENELOPE-B) (NCT01864746). US Institutes of Health, 2016. https://clinicaltrials.gov/ct2/show/NCT01864746, accessed January 5, 2017.

41 ClinicalTrials.gov. Palbociclib collaborative adjuvant study: a randomized phase III trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+)/human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (PALLAS) (NCT02513394). US National Institutes of Health, 2016. https://clinicaltrials.gov/ct2/show/NCT02513394?term=PALLAS&rank=1, accessed January 5, 2017.

42 Sun W, Wang DD. A population pharmacokinetic (PK) analysis of palbociclib (PD-0332991) in patients (pts) with advanced solid tumors [abstract 462P]. Ann Oncol 2014;25:iv154.

Figure Legends

Figure 1. Investigator-assessed PFS by treatment for the intent-to-treat subpopulations of (A) premenopausal women, (B) premenopausal women, age ≤50 years, and (C) postmenopausal women age ≤50 years. PFS was defined as the time from the date of randomization to the date or the first documentation of objective progression of disease or death due to any cause in the absence of documented progressive disease, whichever occurred first. PFS data were censored on the date of the last tumor assessment on study for patients who did not have objective tumor progression and who did not die while on study. CI was calculated based on the Brookmeyer and Crowley method.[25]

CI, confidence interval; NE, not estimable; PFS, progression-free survival.

Figure 2. Investigator-assessed confirmed objective response and clinical benefit rate in premenopausal women.

CBR, clinical benefit response; CI, confidence interval; CR, complete response; OR, odds ratio; ORR, objective response rate; PR, partial response; SD, stable disease ≥24 week.

[a]1-sided exact test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomization.

[b]CBR was CR or PR or stable disease ≥24 weeks.

[c]CI was calculated using the exact (Clopper-Pearson) method.[26]

Figure 3. Biochemical plasma analyses for premenopausal women on day 15.

Abbreviations: E2, estradiol; FSH, follicle-stimulating hormone; IQR, interquartile range; LH, luteinizing hormone; max, maximum; min, minimum.

[a]Six patients had E2 concentrations that were not considered valid (ie, below the quantification limit of 1.25 pg/mL or a volume too small for reanalysis).

Tables

Table 1. Baseline Patient and Disease Characteristics for Premenopausal and Postmenopausal Patients Randomly Assigned in PALOMA-3

	Premenopausal (n=108)		Postmenopausal (n=413)		Total (N=521)[a]
	Palbociclib + Fulvestrant (n=72)	Placebo + Fulvestrant (n=36)	Palbociclib + Fulvestrant (n=275)	Placebo + Fulvestrant (n=138)	
Characteristic	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	
Age, y					
≤40	25 (34.7)	8 (22.2)	7 (2.5)	2 (1.4)	42 (8.1)
>40–50	29 (40.3)	21 (58.3)	47 (17.1)	24 (17.4)	121 (23.2)
>50	18 (25.0)	7 (19.4)	221 (80.4)	112 (81.2)	358 (68.7)
Race					

Asian	31 (43.1)	13 (36.1)	43 (15.6)	18 (13.0)	105 (20.2)
White	37 (51.4)	21 (58.3)	215 (78.2)	112 (81.2)	385 (73.9)
Black and other	4 (5.6)	2 (5.6)	17 (6.2)	8 (5.8)	31 (6.0)
Measurable disease present[b]					
Yes	55 (76.4)	26 (72.2)	213 (77.5)	112 (81.2)	406 (77.9)
No	17 (23.6)	10 (27.8)	62 (22.6)	26 (18.8)	115 (22.1)
Visceral disease					
Yes	45 (62.5)	23 (63.9)	161 (58.5)	82 (59.4)	311 (59.7)
No	27 (37.5)	13 (36.1)	114 (41.5)	56 (40.6)	210 (40.3)
Prior lines of endocrine therapy					
1	34 (47.2)	17 (47.2)	126 (45.8)	74 (53.6)	251 (48.2)
2	31 (43.1)	13 (36.1)	109 (39.6)	48 (34.8)	201 (38.6)
≥3	7 (9.7)	6 (16.7)	40 (14.5)	16 (11.6)	69 (13.2)
Prior lines of therapy in					

advanced/metastatic setting					
0	18 (25.0)	9 (25.0)	56 (20.4)	31 (22.5)	114 (21.9)
1	24 (33.3)	17 (47.2)	117 (42.6)	66 (47.8)	224 (43.0)
2	23 (31.9)	7 (19.4)	71 (25.8)	30 (21.7)	131 (25.1)
≥3	7 (9.7)	3 (8.3)	31 (11.3)	11 (8.0)	52 (10.0)
Purpose of most recent treatment	72 (100)	36 (100)	275 (100)	137 (99.3)	520 (99.8)
Adjuvant therapy	18 (25.0)	9 (25.0)	56 (20.4)	31 (22.5)	114 (21.9)
Advanced or metastatic breast cancer	54 (75.0)	27 (75.0)	219 (79.6)	106 (76.8)	406 (77.9)
Disease-free interval, mo	49 (68.1)	25 (69.4)	184 (66.9)	98 (71.0)	356 (68.3)
>24	38 (52.8)	20 (55.6)	154 (56.0)	81 (58.7)	293 (56.2)
12–24	10 (13.9)	5 (13.9)	20 (7.3)	14 (10.1)	49 (9.4)
<12[c]	1 (1.4)	0	10 (3.6)	3 (2.2)	14 (2.7)
Prior endocrine therapy[d]					
Aromatase inhibitors only	1 (1.4)	2 (5.6)	136 (49.5)	68 (49.3)	207 (39.7)

Tamoxifen only	38 (52.8)	17 (47.2)	13 (4.7)	6 (4.3)	74 (14.2)
Aromatase inhibitors and tamoxifen	33 (45.8)	17 (47.2)	126 (45.8)	64 (46.4)	240 (46.1)
Most recent therapy[e]					
Aromatase inhibitors + LHRH	3 (4.2)	1 (2.8)	0	0	4 (<1.0)
Tamoxifen + LHRH	2 (2.8)	1 (2.8)	0	1 (0.7)	4 (<1.0)
Tamoxifen	31 (43.1)	14 (38.9)	28 (10.2)	13 (9.4)	86 (16.5)
Previous chemotherapy in metastatic setting[f]					
Treatment of metastatic disease ± neoadjuvant therapy	23 (31.9)	12 (33.3)	90 (32.7)	52 (37.7)	177 (34.0)
Previous sensitivity to endocrine therapy[g]					
Yes	51 (70.8)	25 (69.4)	223 (81.1)	111 (80.4)	410 (78.7)

No	21 (29.2)	11 (30.6)	52 (18.9)	27 (19.6)	111 (21.3)
Biomarker status by local assessment	67 (100)	34 (100)	265 (100)	127 (100)	493 (100)
ER+/PR+	49 (68.1)	25 (69.4)	191 (69.5)	86 (62.3)	351 (67.4)
ER+/PR–	18 (25.0)	9 (25.0)	74 (26.9)	41 (29.7)	142 (28.8)
PI3K mutation status by cfDNA[h]	53 (100)	26 (100)	212 (100)	104 (100)	395 (100)
Positive	22 (41.5)	9 (34.6)	63 (29.7)	35 (33.7)	129 (32.7)
Negative	31 (58.5)	17 (65.4)	149 (70.3)	69 (66.3)	266 (67.3)
ESR1 mutation status by cfDNA[h]	53 (100)	26 (100)	212 (100)	105 (100)	396 (100)
Positive	9 (17.0)	6 (23.1)	58 (27.4)	33 (31.4)	106 (26.8)
Negative	44 (83.0)	20 (76.9)	154 (72.6)	71 (67.6)	289 (73.0)

Abbreviations: cfDNA, circulating free DNA; ER, estrogen receptor; ESR1, estrogen receptor 1; LHRH, luteinizing hormone-releasing hormone; *PI3K*, phosphoinositide 3-kinase; PR, progesterone receptor.

[a]Due to rounding, some percentages may not total to exactly 100%.

[b]At least 1 target lesion ≥20 mm by conventional techniques or at least 1 target lesion >10 mm for spiral CT.

[c]One subject with negative duration included in <12 months category.

[d]Premenopausal women had to have documented progression while on or within 12 months of completion of adjuvant therapy with tamoxifen whereas postmenopausal women had to have similarly progressed on an aromatase inhibitor.

[e]Values are mutually exclusive. Not all most recent prior therapies are shown.

[f]Subjects are counted for each treatment of metastatic disease (± neoadjuvant) received.

[g]Sensitivity to prior hormonal therapy was defined as either (i) documented clinical benefit (complete response, partial response, stable disease ≥24 weeks) to ≥1 prior hormonal therapy in the metastatic setting, or (ii) ≥24 months of adjuvant hormonal therapy prior to recurrence.

[h]Not all patients had cfDNA samples; the data represent a subset of patients only.

Table 2. Multivariate Analyses of the Association of Baseline[a]/Prognostic Factors With Progression-Free Survival

	Premenopausal[b]			Postmenopausal		
Treatment	**Palbociclib + Fulvestrant (n=72)**	**Placebo + Fulvestrant (n=36)**		**Palbociclib + Fulvestrant (n=275)**	**Placebo + Fulvestrant (n=138)**	
Subjects Who Had Disease Progression or Death, No. (%)	30 (41.7)	23 (63.9)		115 (41.8)	91 (65.9)	
	Hazard Ratio[c]	**95% CI**	***P*[d]**	**Hazard Ratio[c]**	**95% CI**	***P*[d]**
Baseline/prognostic factors						
Treatment arm						
Palbociclib vs placebo	0.495	0.287–0.855	.0117	0.442	0.335–0.584	**<.0001**
Visceral disease						
Yes vs no	2.751	1.422–5.325	.0027	1.708	1.279–2.283	**.0003**
Race						

Asian vs non-Asian (white, black, and other)	0.485	0.270–0.870	.0152

Abbreviations: AI, aromatase inhibitor; CI, confidence interval; NA, not available.

Palbociclib arm, palbociclib + fulvestrant; placebo arm, placebo + fulvestrant.

[a]Baseline factors that entered the model selection included visceral disease (yes vs no), time from first diagnosis to relapse (≤24 months vs >24 months vs NA), prior treatment (AIs vs non-AIs), prior chemotherapy (yes vs no), prior endocrine therapy (1 line vs >1 line), race (Asian vs non-Asian [white, black and other]).

[b]Premenopausal status is per randomization.

[c]A hazard ratio <1 indicates a reduced hazard in the first category, whereas a hazard ratio >1 indicates a reduced hazard on the last category of the variable.

[d]2-sided *P* value, bold indicates significant at the threshold of *P*<.05.

Table 3. Summary and Listing of Treatment-Emergent AEs (All Causalities, All Cycles) Occurring in ≥10% Patients in Any Treatment Arm and Dose Modifications Due to AEs by Menopausal Subgroup and Treatment

	Premenopausal		Postmenopausal	
	Palbociclib + Fulvestrant (n=71)	**Placebo + Fulvestrant (n=36)**	**Palbociclib + Fulvestrant (n=274)**	**Placebo + Fulvestrant (n=136)**
AEs, %[ab]				
Any AEs	98.6	97.2	98.5	87.5
All grade 3/4 AEs	83.1	25.0	71.2	22.1
Any serious AEs	14.1	19.4	12.4	16.9
All grade 3/4 serious AEs	8.5	8.3	9.1	11.8
Dose modifications due to AEs, %				
Dose interruption	90.1	58.3	82.1	62.5
Dose reduction	42.3	2.8	31.8	1.5
Cycle delay	52.1	22.2	46.7	8.8
Discontinuation rate of palbociclib/placebo	5.6	0	4.7	3.7

Average daily dose of palbociclib/placebo, mg[c]												
Median (range)	125 (85–126)			125 (110–126)			125 (80–131)			125 (106–129)		
AEs, %[ab]	All Gr[e]	Gr 3	Gr 4	All Gr	Gr 3	Gr 4	All Gr[e]	Gr 3	Gr 4	All Gr[e]	Gr 3	Gr 4
Hematologic[d]												
Neutropenia	85.9	60.6	15.5	5.6	0	0	79.6	53.3	8.4	2.9	0	0.7
Leukopenia	56.3	32.4	1.4	2.8	0	0	47.8	25.5	0.4	4.4	0.7	0.7
Anemia	21.1	2.8	0	5.6	0	0	29.6	2.9	0	12.5	2.2	0
Thrombocytopenia	19.7	2.8	0	—	—	—	21.5	1.5	0.7	—	—	—
Nonhematologic												
Infections[d]	47.9	1.4	1.4	33.3	2.8	0	40.1	1.8	0	29.4	2.9	0
Nausea	40.8	0	—	36.1	0	—	30.3	0	—	25.0	0.7	—
Stomatitis[d]	36.6	1.4	0	16.7	0	0	24.8	0.4	0	12.5	0	0
Fatigue	35.2	0	—	30.6	0	—	40.1	2.9	—	27.9	1.5	—
Diarrhea	26.8	0	0	16.7	2.8	0	20.1	0	0	19.1	0	0
Vomiting	23.9	0	0	25.0	0	0	15.0	0.4	0	11.8	0.7	0
Headache	22.5	0	—	25.0	0	—	23.4	0.7	—	17.6	0	—
Back pain	21.1	0	—	22.2	5.6	—	13.1	1.5	—	15.4	0.7	—

Arthralgia	19.7	0	—	16.7	0	—	12.8	0.4	—	15.4	0	—
Constipation	19.7	0	0	19.4	0	0	19.0	0	0	14.7	0	0
Decreased appetite	16.9	0	0	11.1	0	0	14.6	1.1	0	7.4	0.7	0
Rash[d]	16.9	0	0	2.8	0	0	14.6	0.7	0	5.9	0	0
Alopecia	15.5	—	—	5.6	—	—	17.5	—	—	6.6	—	—
Hot flush	15.5	0	—	16.7	0	—	15.3	0	—	16.9	0.7	—
Pyrexia	15.5	0	0	13.9	0	0	9.9	0.4	0	2.9	0	0
Dizziness	14.1	1.4	—	16.7	0	—	11.3	0	—	7.4	0	—
Insomnia	14.1	1.4	—	5.6	0	0	8.4	0	0	7.4	0	0
Oropharyngeal pain	14.1	0	0	11.1	0	0	9.9	0	0	5.9	0	0
Cough	11.3	0	—	13.9	0	—	15.7	0	—	12.5	0	—
Abdominal pain upper	2.8	0	0	16.7	0	0	—	—	—	5.1	0	0
Abdominal pain	7.0	0	—	13.9	0	—	8.4	0.7	—	3.7	0.7	—
Injection site pain	2.8	0	0	13.9	0	0	7.3	0.4	0	8.8	0	0
Pain in extremity	8.5	0	—	13.9	2.8	—	13.5	0	—	11.8	1.5	—
Asthenia	2.8	0	0	11.1	0	0	8.0	0	0	3.7	0.7	0
Chest pain	1.4	0	—	11.1	0	—	2.6	0.4	—	5.1	0	—

Abbreviations: AE, adverse event; Gr, grade; n, subjects evaluable for AEs (ie, includes all patients who received ≥1 dose of study treatment [palbociclib/placebo or fulvestrant]); PT, preferred term.

[a]Percentages are calculated in reference to n, and values include data up to 28 days after the last dose of study drug.

[b]Events coded using the Medical Dictionary for Regulatory Activities (version 18.0) PTs, including clusters of PTs, and by maximum Common Terminology Criteria for Adverse Events grade.

[c]Average daily dose administered = (total dose administered)/(total days on drug). Days on drug is defined as the total number of days on which the drug was actually administered.

[d]Clustered PTs: Anemia refers to any event having a PT equivalent to anemia or hematocrit decreased or hemoglobin decreased; infections is any event having a PT part of the system organ class infections and infestations; leukopenia is any event having a PT equivalent to leukopenia or white blood cell count decreased; neutropenia is any event having a PT equivalent to neutropenia or neutrophil count decreased. Rash is any event having a PT equivalent to dermatitis or dermatitis acneiform or rash or rash erythematous or rash maculopapular or rash papular or rash pruritic; stomatitis is any event having a PT equivalent to aphthous stomatitis or cheilitis or glossitis or glossodynia or mouth ulceration or mucosal inflammation or oral pain or oropharyngeal discomfort or oropharyngeal pain or stomatitis; thrombocytopenia is any event having a PT equivalent to platelet count decreased or thrombocytopenia.

[e]Grade 5 events: in the palbociclib plus fulvestrant arm of the study, 2 (2.8%) premenopausal women had disease progression, and 1 (1.4%) premenopausal woman with disease progression also had hepatic failure; among postmenopausal women in the palbociclib plus fulvestrant arm, 1 (0.4%) had disseminated intravascular coagulation and 1 (0.4%) experienced general or physical health deterioration; among postmenopausal women in the placebo arm of the study, 1 (0.7%) had acute respiratory distress, 1 (0.7%) had breast cancer, and 1 (0.7%) had a cerebral hemorrhage.

FIGURES

Fig 1.

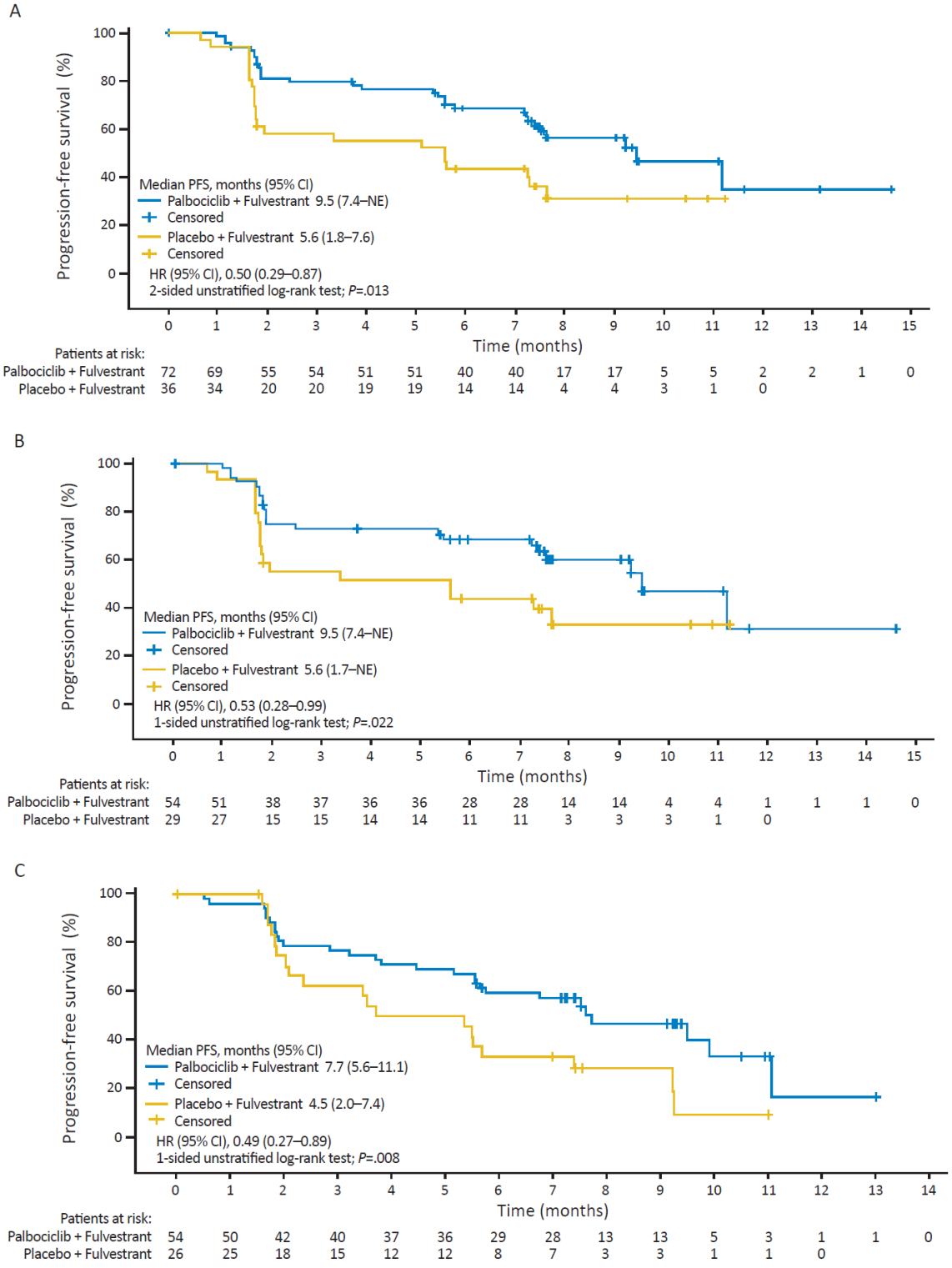
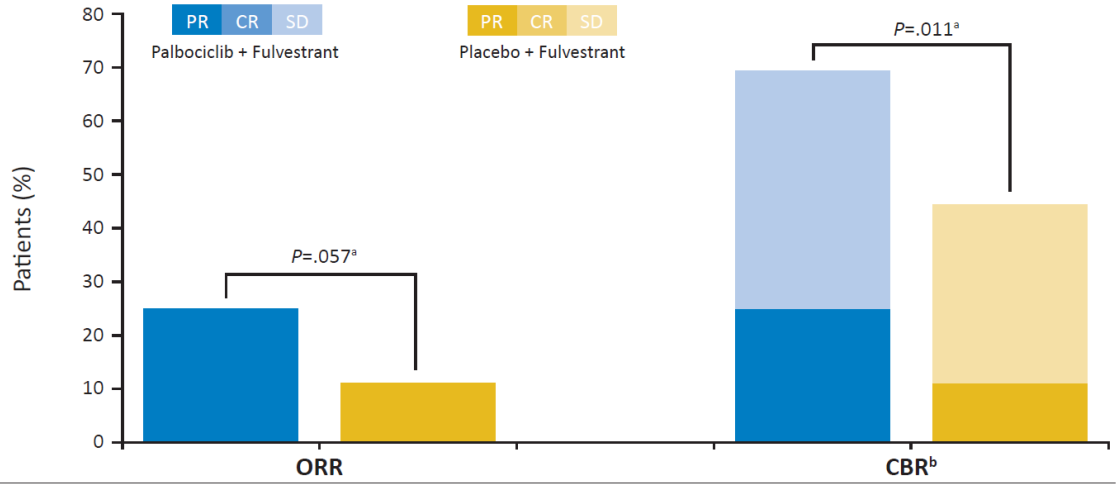
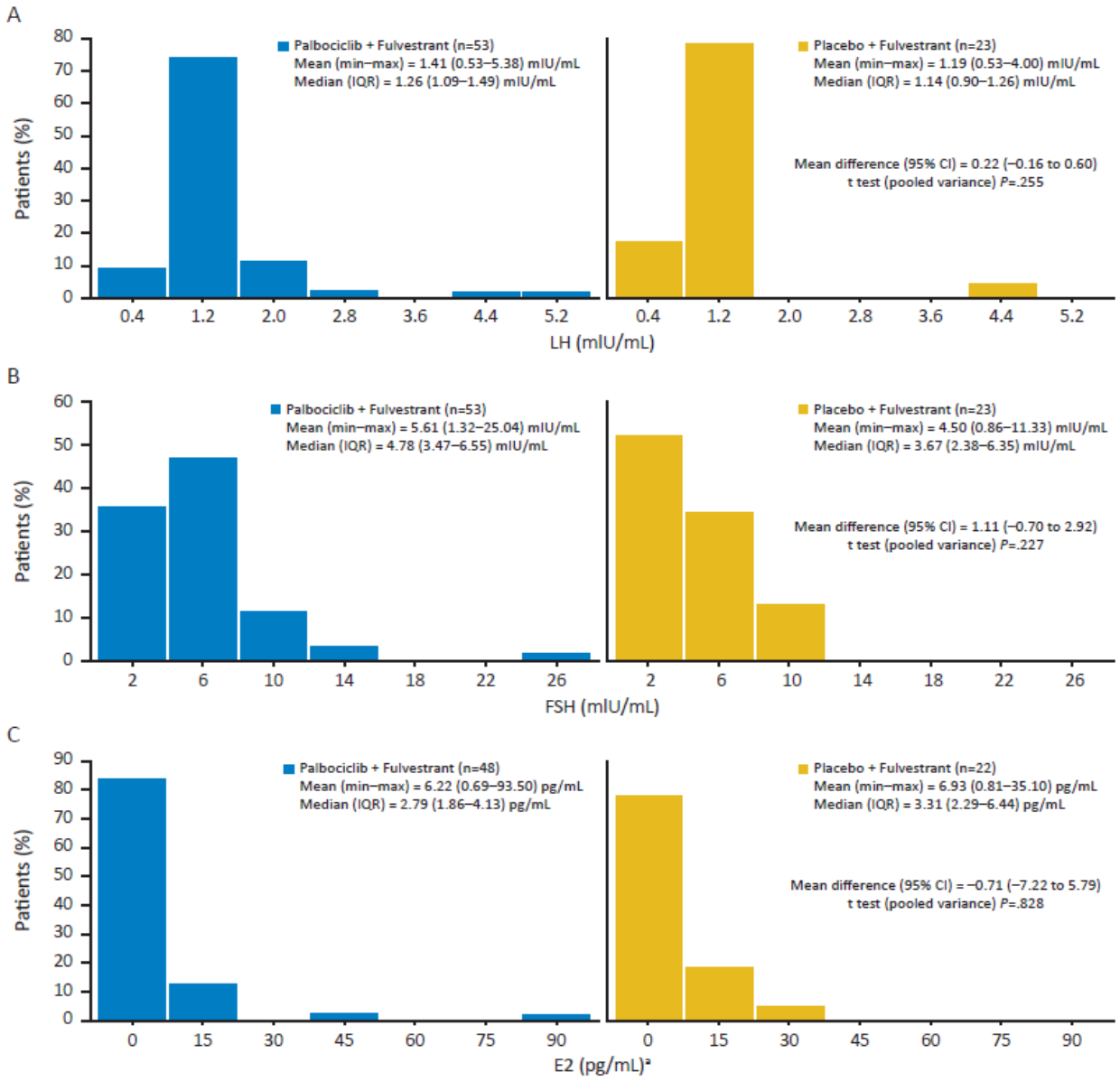


Fig 2.



Population:	Premenopausal	Premenopausal
OR (95% CI)[c]	3.06 (0.82–13.38)	2.89 (1.15–7.34)

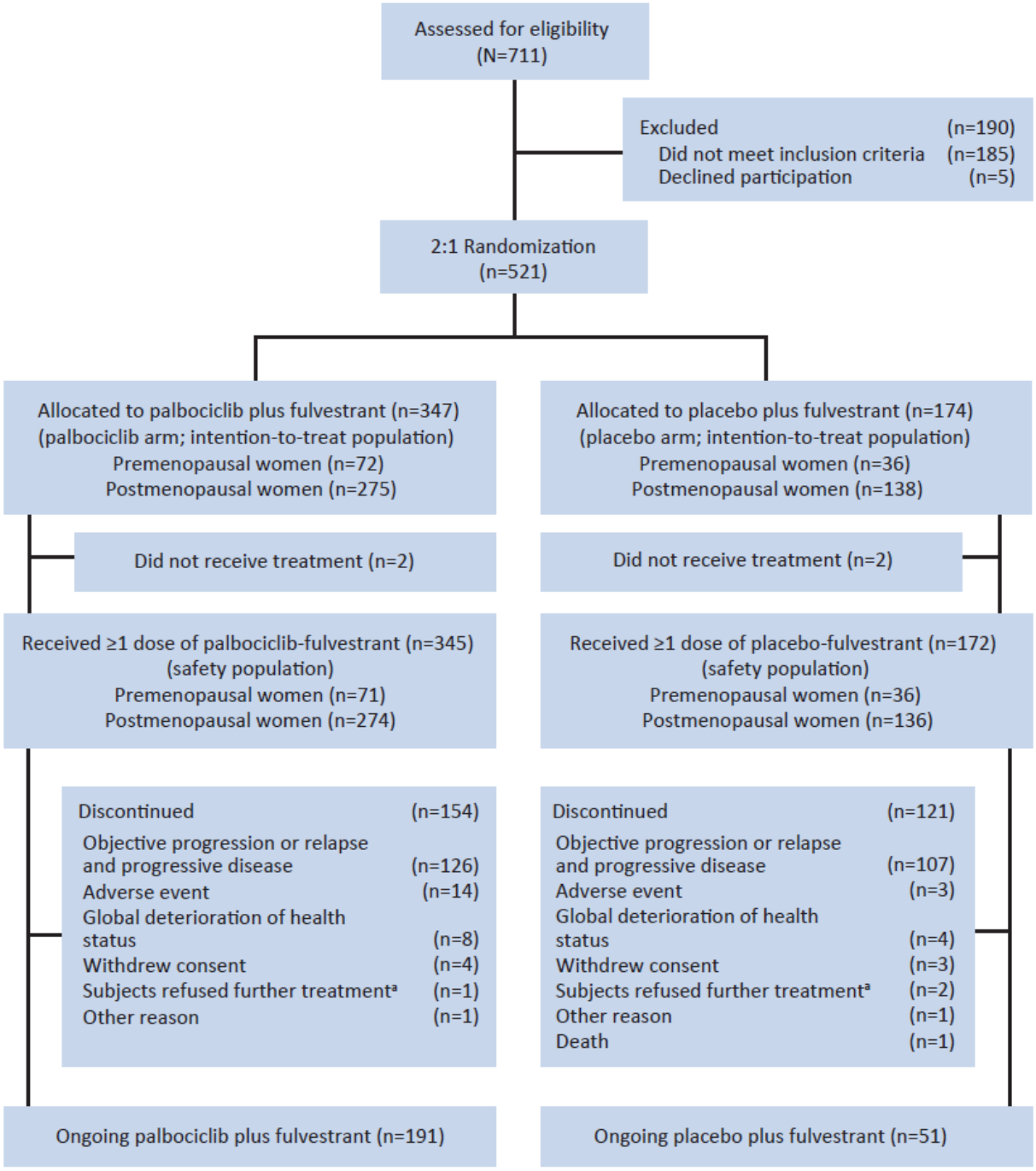
Fig 3.


A
Palbociclib + Fulvestrant (n=53)
Mean (min–max) = 1.41 (0.53–5.38) mIU/mL
Median (IQR) = 1.26 (1.09–1.49) mIU/mL
Placebo + Fulvestrant (n=23)
Mean (min–max) = 1.19 (0.53–4.00) mIU/mL
Median (IQR) = 1.14 (0.90–1.26) mIU/mL
Mean difference (95% CI) = 0.22 (–0.16 to 0.60)
t test (pooled variance) P=.255
Patients (%)
LH (mIU/mL)
B
Palbociclib + Fulvestrant (n=53)
Mean (min–max) = 5.61 (1.32–25.04) mIU/mL
Median (IQR) = 4.78 (3.47–6.55) mIU/mL
Placebo + Fulvestrant (n=23)
Mean (min–max) = 4.50 (0.86–11.33) mIU/mL
Median (IQR) = 3.67 (2.38–6.35) mIU/mL
Mean difference (95% CI) = 1.11 (–0.70 to 2.92)
t test (pooled variance) P=.227
Patients (%)
FSH (mIU/mL)
C
Palbociclib + Fulvestrant (n=48)
Mean (min–max) = 6.22 (0.69–93.50) pg/mL
Median (IQR) = 2.79 (1.86–4.13) pg/mL
Placebo + Fulvestrant (n=22)
Mean (min–max) = 6.93 (0.81–35.10) pg/mL
Median (IQR) = 3.31 (2.29–6.44) pg/mL
Mean difference (95% CI) = –0.71 (–7.22 to 5.79)
t test (pooled variance) P=.828
Patients (%)
E2 (pg/mL)a

Appendix

Figure A1. CONSORT diagram (online only)

[a]For reasons other than an adverse event.



Supplementary Text

Drug-Drug Interactions

Potential for drug-drug interactions (DDIs) on the analytes palbociclib, fulvestrant, and goserelin was assessed using a 1-way analysis of variance (ANOVA) to analyze the natural log-transformed C_{trough} with unique drug combination as a single factor. Additionally, the potential for DDIs to affect the PK of palbociclib was assessed using an analysis of covariance (ANCOVA) model to analyze the natural log-transformed C_{trough} with unique drug combination as a main effect along with age and baseline body weight, the only covariates found to be statistically significant in a prior palbociclib population PK model,[42] were covariates in the full model. Regression analyses were performed on the natural log-transformed C_{trough} against unique drug combinations, and covariates identified using a backward selection process remained in the final ANCOVA model. The input for each statistical model was the within-patient mean of 2 steady-state (SS) $C_{troughs}$ for each analyte. For analyses using palbociclib PK, data from PALOMA-3 comprised the test group and historical data comprised the reference group. For analyses using fulvestrant and goserelin, PK comparisons were made across palbociclib and placebo treatment arms. A data cutoff of December 5, 2014 was used for the analyses of potential DDIs.

Table A1. Statistical Summary of Treatment Comparisons for Within-Patient Mean $C_{troughSS}$, Assessment of DDI Potential Between Palbociclib, Fulvestrant, and Goserelin (PALOMA-3; online only)

Statistical Model	Adjusted Geometric Means[a]		Ratio (Test/Reference) of Adjusted Means[b]	90% CI for Ratio[b]
	Test Group	Reference Group		
Potential Effect of Goserelin on Palbociclib PK				
	Palbociclib + Fulvestrant + Goserelin (n=43)	**Palbociclib + Fulvestrant – Goserelin (n=174)**		
ANOVA[c]	72.0	79.7	90.4	(80.2–102)
ANCOVA, full[d]	73.9	79.4	93.1	(81.9–106)
ANCOVA, final[e]	70.6	80.0	88.3	(78.6–99.1)
Potential Effect of Fulvestrant on Palbociclib PK				
	Palbociclib + Fulvestrant Total (n=217)	**Palbociclib Historical Data[f] (n=98)**		
ANOVA[c]	75.8	58.8	129	(118–141)
ANCOVA, full[d]	76.6	58.6	131	(119–143)
ANCOVA, final[e]	75.2	58.9	128	(117–140)
Potential Effect of Goserelin on Fulvestrant PK				
	Palbociclib + Fulvestrant + Goserelin (n=9)	**Palbociclib + Fulvestrant − Goserelin (n=28)**		
ANOVA[c]	11.1	10.7	103	(79.6–134)

Statistical Model	Adjusted Geometric Means[a]		Ratio (Test/Reference) of Adjusted Means[b]	90% CI for Ratio[b]
	Test Group	Reference Group		
	Placebo + Fulvestrant + Goserelin (n=5)	**Placebo + Fulvestrant − Goserelin (n=14)**		
ANOVA[c]	10.4	8.4	124	(87.1–176)
Potential Effect of Palbociclib on Fulvestrant PK				
	Palbociclib + Fulvestrant Total (n=37)	**Placebo + Fulvestrant Total (n=19)**		
ANOVA[c]	10.8	8.85	122	(101–147)
Potential Effect of Palbociclib on Goserelin PK				
	Palbociclib + Fulvestrant + Goserelin (n=9)	**Placebo + Fulvestrant + Goserelin (n=5)**		
ANOVA[c]	303	274	110	(54.2–225)

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CI, confidence interval; $C_{troughSS}$, steady-state concentration trough; DDI, drug-drug interactions; PK, pharmacokinetics.

One outlier was excluded from final analyses using palbociclib PK because the absolute value of the patient's studentized residual was >5 in all statistical models.

[a]Adjusted geometric means for palbociclib and fulvestrant are presented in units of ng/mL, whereas goserelin is presented in units of pg/mL.

[b]The ratios and 90% CIs are expressed as percentages.

[c]Based on log-transformed ANOVA with final values back-transformed from the log scale. Unique drug combination is the fixed factor.

[d]Based on log-transformed ANCOVA with final values back-transformed from the log scale. Unique drug combination is the fixed factor, with age and baseline weight as the covariates in the full model.
[e]Based on log-transformed ANCOVA with final values back-transformed from the log scale. Unique drug combination is the fixed factor, with baseline weight as the only covariate in the final model.
[f]Historical palbociclib PK data are from studies registered with ClinicalTrials.gov identifiers NCT00141297, NCT00420056, NCT00721409.