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Palbociclib Combinedwith Fulvestrant in Premenopausal Women withAdvanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results

Right Running Head: Loibl, Turner, Ro et al.
Left Running Head: Palbociclib-Fulvestrant for Premenopausal ABC

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Key Words. Palbociclib •Fulvestrant •Goserelin •Breast cancer •Premenopausal •Neoplasm metastasis

ABSTRACT

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

Patients andMethods.One hundred eight premenopausal endocrine-refractory women≥18 years with hormone receptor positive (HR+)/human epidermal growth receptor 2 negative (HER2−)ABC were among 521 womenrandomized 2:1 (347:174) to fulvestrant (500 mg) ± goserelin with either palbociclib (125 mg/day orally, 3 weeks on, 1 week off) or placebo. This analysis assessed whether the overall tolerable safety profile andsignificant 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) versusplacebo arm (*n*=36) was 9.5versus5.6 months, respectively (hazard ratio, 0.50, 95% confidence interval: 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 premenopausaland postmenopausal women in pivotal combination ET

trialsfacilitates access to novel drugs for young women and should be considered as a new standard for clinical trial design.

ClinicalTrials.gov NCT01942135

IMPLICATIONS FOR PRACTICE

PALOMA-3, the first registrational study to include premenopausal women in a trial investigatinga CDK4/6 inhibitor combined with endocrine therapy, hasthe largest premenopausal cohort reported in an endocrine-resistant setting.In pretreated premenopausal women with hormone receptor positiveadvanced breast cancer, palbociclib plus fulvestrant and goserelin(luteinizing hormone-releasing hormone[LHRH] agonist) treatment almost doubled median progression-free survival (PFS) and significantly increasedthe objective response rate versusendocrine monotherapy, achieving results comparable to thosereported forchemotherapy without apparently interfering withLHRHagonist-induced ovarian suppression. The significant PFS gain and tolerable safety profilestrongly supportuse of this regimen in premenopausal women with endocrine-resistant disease who could possiblydelay chemotherapy.

INTRODUCTION

Many women presenting with early breast cancer (BC) are premenopausal;upon relapse with advanced breast cancer(ABC), most are postmenopausal, predominantly as a result of cytotoxic therapy and extended endocrine therapy (ET) treatment[1], or via natural changes. Althoughyounger womenrepresent 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 withthe risk for relapse[3,4].Survival outcomesare also worse for women<40 years than for older age groups,notwithstanding intense treatment regimens[3].

Denovo metastatic and relapsed breast cancercan also occur in peri/premenopausal women(hereafter referred to as premenopausal women)[5,6].Yet premenopausal women have generally been excluded from large registrational trialsinvolving hormonal agents to assess hormone-positiveABC; clinical data for premenopausal women remain remarkablylimited toonly 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 receptorpositive (HR+)human epidermal growth factor receptor 2negative (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 (LHRH) agonist. Although tamoxifen is used as thefirst-line ET for premenopausal women with HR+ BC (preferably with ovarian suppression[14]), aromatase inhibitors (AIs) plus LHRH 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 becauseof limited data supporting its biological effects[17].In a neoadjuvant study of 66 premenopausal women with ER positive (ER+) BC receiving250 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, similarto changesobserved in premenopausal women treated with tamoxifen,suggestinga potential need for higher doses of fulvestrant inpremenopausal 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: letrozolevs. letrozole + palbociclib[21]; PALOMA-2 trial: letrozole + placebovs. letrozole + palbociclib[22]) and in women pretreatedforHR+/HER2−ABC (PALOMA-3 trial: fulvestrantvs. 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 9.5vs. 4.6 months, respectively, hazard ratio [HR], 0.46 [95% confidence interval {CI}: 0.36–0.59], two-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 womenwith prior endocrine-resistant HR+/HER2−ABC.

MATERIALS 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 includewomen ≥18years 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 asage ≥60 years, age <60 years and amenorrheafor ≥12 consecutive months (excluding an alternative pathologic or physiologic cause), and serum estradiol (E2)andfollicle-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/day 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 LHRH agonistsubcutaneouslyevery 28 days starting≥4 weeks before study treatment, and upon starting treatment any patients using aLHRH agonistother thangoserelin 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, http://www.inventivhealth.com) using gas chromatography (GC)/tandem mass spectrometry (MS-MS). The lower limit of quantification was 0.625 pg/mL. Luteinizing hormone(LH) and FSH were measured at the Royal Marsden Hospital byimmunoradiometric

assay (MG12151, IBL International, Hamburg, Germany, http://www.ibl-international.com;KIP0841, DIAsource, Ottignies-Louvain-la-Neuve, Belgium, http://www.diasource-diagnostics.com). 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 1and 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 progression-free survival (mPFS) and generate survival curves. A two-sided unstratified log-rank test was used to compare treatment armsby menopausal status and a one-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 HR was estimated from the Cox proportional hazards regression model. Clinical benefit response (CBR) and objective response ratewere evaluated and compared between treatment arms using a one-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 Student's *t* tests(one for each hormone) wereused to compare data between treatment armswithout 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(supplemental online Appendix 1).Statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC, https://www.sas.com/en_us/home.html).

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 October7, 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(supplemental online Fig. 1A)[6].

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.

Amongpostmenopausal 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 wellbalanced, except more premenopausal womenhad twoprior 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 wellbalanced, although the *ESR1*mutation rate by cfDNA was slightly lower in premenopausal women.

Efficacy

The data cutoff for this analysis was March 16, 2015, correspondingwith the final primary efficacy analysis of PFS for the overall intent-to-treat population[6].Investigator-assessed mPFS for palbociclib plus fulvestrantversusplacebo plus fulvestrant in the premenopausal subgroup was 9.5versus 5.6 months, respectively (HR,0.50 [95% CI: 0.29–0.87], two-sided p =.013). In the postmenopausal subgroup,mPFSwas 9.9versus3.9 months (HR,0.45 [0.34–0.59], two-sided p <.0001). Kaplan-Meier survival curves for PFS are shown for premenopausal women in Fig.1[25].

In the palbociclibarmversus the placebo arm, investigator-assessed objective responses were observed in 25.0% (18/72)versus 11.1% (4/36) of premenopausal patients, respectively (odds ratio [OR], 3.06 [95% CI: 0.82–13.38], p =.057;Fig. 2) [26]. Significant improvement occurred with palbociclib plus fulvestrant versusplacebo plus fulvestrant in investigator-assessed CBR, which was observed in 69.4% (50/72) versus44.4% (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 Findingsin Pre- and Postmenopausal Women≤50 Years Old

Amongpremenopausal women aged ≤50 years (*n*=83), mPFS was 9.5 months in the palbociclib arm and 5.6 months in the placebo arm(HR, 0.53 [95% CI: 0.28–0.99], one-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 7.7versus4.5 months, respectively (HR, 0.49 [0.27–0.89], one-sided unstratified log-rank test,*p* =.008; Fig 1C).

Prognostic Factors

Important and favorable prognostic factors in the final Cox proportional hazardsmultivariate model included absence of visceral disease for both premenopausal and postmenopausal patient subpopulations and Asian ethnicityfor 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 body mass index (BMI) was examined with the treatment arm in a separate multivariate model, lower values weremore favorable for PFS.

Safety

Althoughall premenopausal women receivedgoserelin concurrently with palbociclibplus fulvestrant, the safety profile wassimilar 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, and cycle delays.Dose interruptions and discontinuation rate due to AEs were alsosimilar 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 Student's *t*tests were >.05(Fig. 3).Mean E2 concentrations were consistent with those expected in the postmenopausal range. One patient in thepalbociclib 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 BMIin both treatment arms (Spearman's rho= .44, p =.002 and .49, p =.02, respectively).

Drug-Drug Interaction Assessment

Results of the1-way analysis of variance (ANOVA) and analysis of covariance(ANCOVA) analyses conducted to investigate the potential for DDIs amongpalbociclib, fulvestrant, and goserelin are shown in the table in supplemental online Appendix 1.The ratio of the adjusted geometric means (90% CI) for palbociclib from the final ANCOVA model andthe 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 withprior endocrine-resistant HR+/HER2−ABC ever studied. The study found thatpremenopausal patients who received palbociclib plus fulvestrantsignificantly benefited compared with patients treated with placebo plus fulvestrant, consistent with the benefit observed forpostmenopausal women. Inpremenopausal and postmenopausal women aged ≤50 years, PFS favored the palbociclib arm compared with the placebo arm, regardless of menopausal status and LHRH 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 twofold 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 anLHRH 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 reportedto 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 LHRH agonists[7,8,31].The addition of a LHRH agonist to tamoxifen or AIs has been shown to improve efficacy in early BC 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 U.S.Food and Drug Administrationwas recently expanded to include premenopausal women who receive concurrentovarian 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 PKdata confirm there were no clinically significant metabolic DDIs between palbociclib and goserelin or between palbociclib and fulvestrant when thesetwodrugs were coadministered.Furthermore, thecoadministration of goserelin did not have a clinically significant impact on fulvestrant plasma PK.

The clinical effectiveness of LHRH 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 firstmonth of treatment, partial recovery can occur in some patients, apparently driven by progressive recovery of FSH levels[35].Combining a LHRH agonistwith fulvestrant could still potentially result in incomplete ovarian suppression ifE2 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 that 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 fulvestranthad an E2 value that was clearly premenopausal;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 andBMI;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 LHRH 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 palbociclibwere also similar between premenopausal and postmenopausal groups.

CONCLUSION

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 National Comprehensive Cancer Network[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 LHRH 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 goserelinfor women with HR+ ABC, and these findings have expanded the treatment options for premenopausal women.

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DISCLOSURES

The authors indicated no financial relationships.

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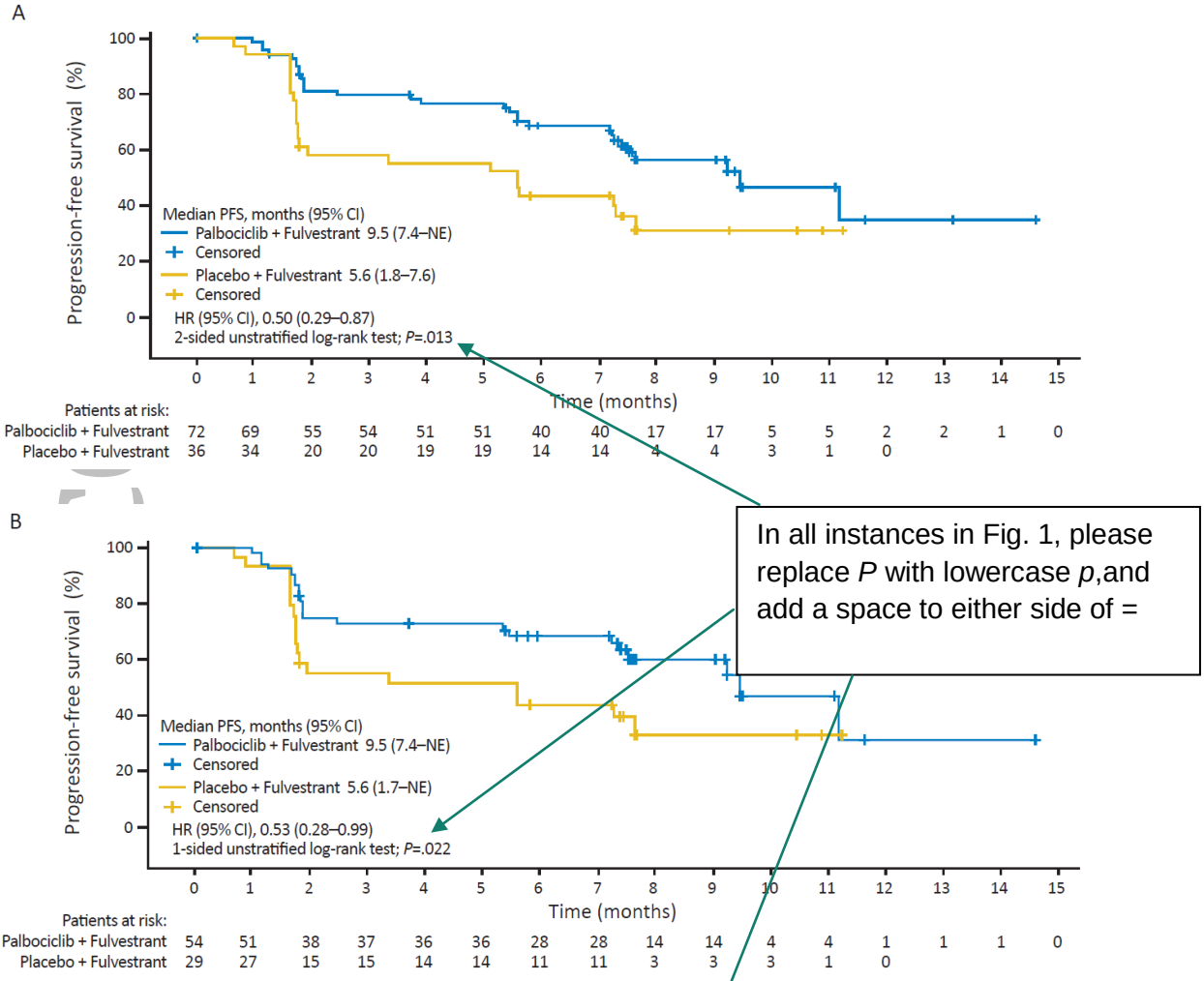
Figure 1. Investigator-assessed PFS by treatmentfor the intent-to-treat subpopulations of premenopausal women**(A)**, premenopausal women**(B)**, age ≤50 years, and postmenopausal women age ≤50 years**(C)**. PFS was defined as the time from the date of randomization to the date or the first documentation 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].

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



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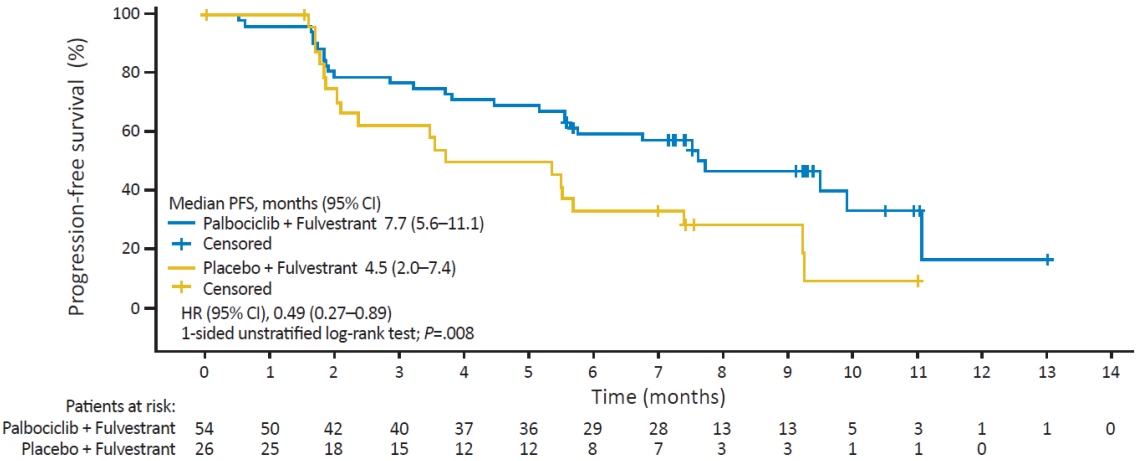

Patients at risk:														
Palbociclib + Fulvestrant	54	50	42	40	37	36	29	28	13	13	5	3	1	1	0
Placebo + Fulvestrant	26	25	18	15	12	12	8	7	3	3	1	1	0		

Figure 2. Investigator-assessed confirmed objective response and clinical benefit rate in premenopausal women. [a]One-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].
Abbreviations: 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.

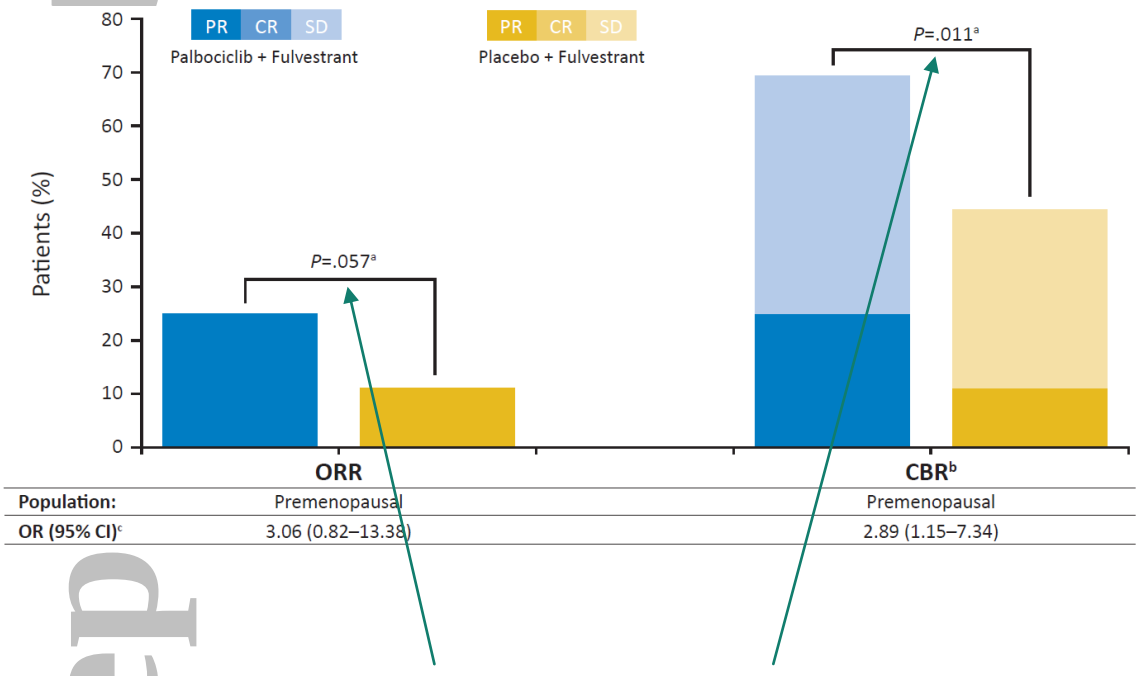

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Figure 3. Biochemical plasma analyses for premenopausal women on day 15.

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

Abbreviations: CI, confidence interval;E2, estradiol; FSH, follicle-stimulati

interquartile range; LH, luteinizing hormone; max, maximum; min, minimu

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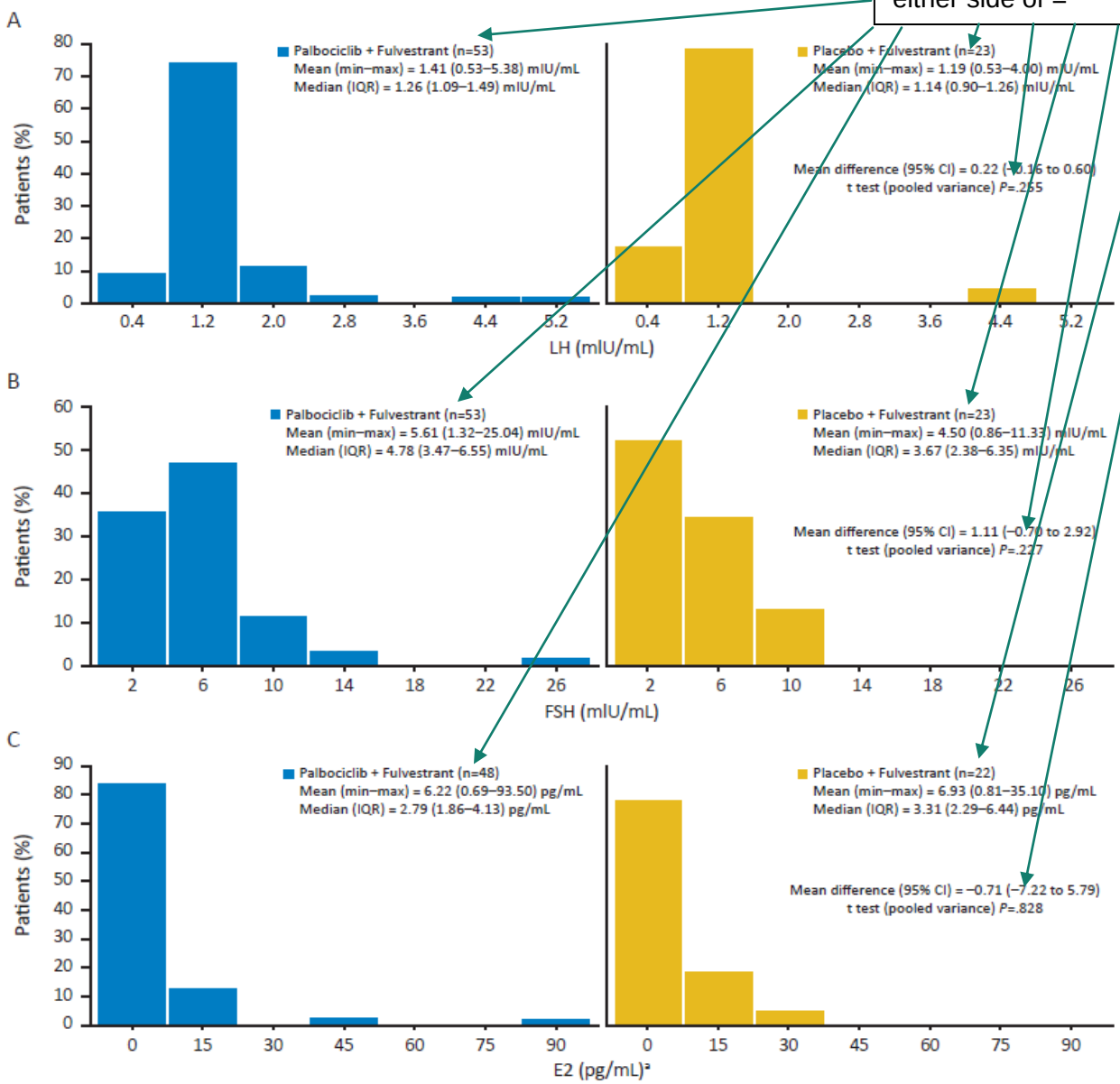

Table 1. Baseline patient and disease characteristics for premenopausal and postmenopausal patients randomly assigned in PALOMA-3

	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	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	
Age, years					
≤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, months	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	1 (1.4)	2 (5.6)	136 (49.5)	68 (49.3)	207 (39.7)

only					
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)

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

[b]At least one target lesion ≥20 mm by conventional techniques or at least one target lesion >10mm 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 mutuallyexclusive. 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 (a) documented clinical benefit (complete response, partial response, stable disease≥24 weeks) to ≥1 prior hormonal therapy in the metastatic setting, or (b) ≥24 months of adjuvant hormonal therapy prior to recurrence.

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

Abbreviations: cfDNA, circulating free DNA; CT, computed tomography;ER+, estrogen receptor positive; *ESR1*, estrogen receptor 1; LHRH, luteinizing hormone-releasing hormone;*PI3K*, phosphoinositide 3-kinase; PR+, progesterone receptor positive; PR−, progesterone receptor negative.

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, *n* (%)	30 (41.7)	23 (63.9)		115 (41.8)	91 (65.9)	
	Hazard ratio[c]	**95% CI**	***p*value[d]**	**Hazard ratio[c]**	**95% CI**	***p*value[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						
Yesvs.no	2.751	1.422–5.325	.0027	1.708	1.279–2.283	**.0003**
Race						

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

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

[a]Baseline factors that entered the model selection included visceral disease (yesvs.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), andrace (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]Two-sided*p*value, bold indicates significant at the threshold of $p < .05$.

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

	Premenopausal		Postmenopausal	
	Palbociclib + Fulvestrant (*n*=71)	**Placebo + Fulvestrant (*n*=36)**	**Palbociclib + Fulvestrant (*n*=274)**	**Placebo + Fulvestrant (*n*=136)**
AEs, %[a,b]				
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)

Table 3. Summary and listing of treatment-emergent AEs (all causalities, all cycles)

AEs, %[a,b] occurring in ≥10% patients in any treatment arm and dose modifications due to AEs by menopausal status[d] and treatment	All Gr[e]	Gr 3	Gr 4	All Gr[e]	Gr 3	Gr 4	All Gr[e]	Gr 3	Gr 4	All Gr[e]	Gr 3	Gr 4
Hematologic												

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	14.1	0	0	11.1	0	0	9.9	0	0	5.9	0	0

pain												
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	—

[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 anyevent having a PT part of the system of 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, two(2.8%) premenopausal women had disease progression, and one (1.4%) premenopausal woman with disease progression also had hepatic failure; among postmenopausal women in the palbociclib plus fulvestrant arm, one (0.4%) had disseminated intravascular coagulation and one (0.4%) experienced general or physical health deterioration; among postmenopausal women in the placebo arm of the study, one (0.7%) had acute respiratory distress, one (0.7%) had breast cancer, and one (0.7%) had a cerebral hemorrhage.

Abbreviations: —, no data; AE, adverse event; Gr, grade; ***n***, subjects evaluable for AEs (i.e., includes all patients who received ≥1 dose of study treatment [palbociclib/placebo or fulvestrant]); PT, preferred term.

[TOC summary] In the randomized, phase III PALOMA-3 trial, palbociclib plus fulvestrant (± goserelin) prolonged investigator-assessed progression-free survival compared with placebo plus fulvestrant (± goserelin) in women with HR+/HER2- advanced breast cancer after prior progression on endocrine therapy. PALOMA-3 was the first registrational study to include premenopausal women in this setting; in this article, results are described by menopausal status, with a focus on premenopausal women with prior endocrine-resistant HR+/HER2 advanced breast cancer.