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# Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy in Estrogen Receptor–Positive Early Breast Cancer: PALLET Trial

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abstract

**PURPOSE** CDK4/6 inhibitors are used to treat estrogen receptor (ER)–positive metastatic breast cancer (BC) in combination with endocrine therapy. PALLET is a phase II randomized trial that evaluated the effects of combination palbociclib plus letrozole as neoadjuvant therapy.

**PATIENTS AND METHODS** Postmenopausal women with ER-positive primary BC and tumors greater than or equal to 2.0 cm were randomly assigned 3:2:2:2 to letrozole (2.5 mg/d) for 14 weeks (A); letrozole for 2 weeks, then palbociclib plus letrozole to 14 weeks (B); palbociclib for 2 weeks, then palbociclib plus letrozole to 14 weeks (C); or palbociclib plus letrozole for 14 weeks. Palbociclib 125 mg/d was administered orally on a 21-days-on, 7-days-off schedule. Core-cut biopsies were taken at baseline and 2 and 14 weeks. Coprimary end points for letrozole versus palbociclib plus letrozole groups (A *v* B + C + D) were change in Ki-67 (protein encoded by the *MKI67* gene; immunohistochemistry) between baseline and 14 weeks and clinical response (ordinal and ultrasound) after 14 weeks. Complete cell-cycle arrest was defined as Ki-67 less than or equal to 2.7%. Apoptosis was characterized by cleaved poly (ADP-ribose) polymerase.

**RESULTS** Three hundred seven patients were recruited. Clinical response was not significantly different between palbociclib plus letrozole and letrozole groups ($P = .20$; complete response + partial response, 54.3% *v* 49.5%), and progressive disease was 3.2% versus 5.4%, respectively. Median log-fold change in Ki-67 was greater with palbociclib plus letrozole compared with letrozole ($-4.1$ *v* $-2.2$; $P < .001$) in the 190 evaluable patients (61.9%), corresponding to a geometric mean change of −97.4% versus −88.5%. More patients on palbociclib plus letrozole achieved complete cell-cycle arrest (90% *v* 59%; $P < .001$). Median log-fold change (suppression) of cleaved poly (ADP-ribose) polymerase was greater with palbociclib plus letrozole versus letrozole ($-0.80$ *v* $-0.42$; $P < .001$). More patients had grade 3 or greater toxicity on palbociclib plus letrozole (49.8% *v* 17.0%; $P < .001$) mainly because of asymptomatic neutropenia.

**CONCLUSION** Adding palbociclib to letrozole significantly enhanced the suppression of malignant cell proliferation (Ki-67) in primary ER-positive BC, but did not increase the clinical response rate over 14 weeks, which was possibly related to a concurrent reduction in apoptosis.

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**ASSOCIATED CONTENT**

**Data Supplements**

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Use of endocrine therapy for the treatment of hormone receptor (HR) –positive breast cancer (BC) is a seminal example of successfully targeted cancer treatment. Nonetheless, endocrine therapy resistance, either de novo or acquired, remains a challenge in patients with both early and advanced BC.[1-4] One approach to reverse resistance to standard endocrine therapy has been to target an alternative pathway.

Cyclin-dependent kinases CDK4 and CDK6 promote progression from $G_1$ phase to S phase of the cell cycle. Inhibition of these kinases leads to decreased

proliferation of estrogen receptor (ER) –positive tumors and reverses endocrine resistance in some patients. The CDK4/6 inhibitor, palbociclib (Ibrance; Pfizer, New York, NY), has demonstrated considerable activity when combined with other endocrine therapies in patients with metastatic BC in both first-line and second-line settings,[5-8] with recent results demonstrating prolonged overall survival in the second-line setting.[9] Large, phase III adjuvant BC trials with palbociclib and other CDK4/6 inhibitors are ongoing [PALLAS (ClinicalTrials.gov identifier: NCT02513394) PENELOPE-B (ClinicalTrials.gov identifier: NCT01864746), and MONARCH-E (ClinicalTrials.gov identifier: NCT03155997).

In early BC, use of neoadjuvant therapy is an attractive option to facilitate breast conservation and, critically, enables the assessment of in vivo biomarkers to identify proof-of-principle activity or predict responsive or resistant subgroups of tumors.[10,11] Achievement of a pathologic complete response (pCR) in HR-positive cancers to chemotherapy is less common than in other subtypes of BC. A recent meta-analysis reported similar clinical responses and achievement of breast conservation in HR-positive BC with neoadjuvant endocrine therapy compared with combination chemotherapy, but with lower toxicity.[12] As such, strategies to further improve response to neoadjuvant endocrine therapy in HR-positive cancers are more relevant than using chemotherapy. In HR-positive disease, a decrease in the proliferation marker Ki-67 (protein encoded by the *MKI67* gene) from baseline in response to endocrine therapy has been validated as a marker of treatment benefit, with measurement of Ki-67 after 2 weeks of endocrine therapy shown to improve the prediction of recurrence-free survival (RFS).[13,14] Given the predominantly antiproliferative effects of palbociclib, suppression of Ki-67 is a rational end point for estimating whether there is efficacy with the addition of palbociclib to an aromatase inhibitor (AI) versus AI alone in the neoadjuvant setting.

Here, we report the results of PALLET, a large, multinational, neoadjuvant randomized trial (ClinicalTrials.gov identifier: NCT02296801, ISRCTN31243262), designed with coprimary end points examining the biologic and clinical effects of neoadjuvant letrozole with or without palbociclib for 14 weeks as primary treatment of ER-positive/human epidermal growth factor receptor 2 (HER2) –negative early invasive BC.

## PATIENTS AND METHODS

Full details of the methodology are available in the Data Supplement.

### Trial Design and Patients

PALLET is a phase II randomized multicenter trial with parallel United Kingdom and North American protocols. Patients were recruited from 38 sites in the United Kingdom, United States, and Canada. Eligible patients were postmenopausal women with unilateral, operable, ER-positive, HER2-negative tumors that measured at least 2 cm by ultrasound with no evidence of metastatic disease. ER positivity and HER2 negativity were defined as per ASCO/College of American Pathologists guidelines[15,16] and were locally assessed.

Patients were randomly assigned 3:2:2:2 to one of four treatment groups. Group A received letrozole alone for 14 weeks, group B letrozole for 2 weeks followed by palbociclib plus letrozole to 14 weeks, group C palbociclib for 2 weeks followed by palbociclib plus letrozole to 14 weeks, and group D palbociclib plus letrozole for 14 weeks (Data Supplement). The parallel four-group design with a 2-week change for groups B and C allowed us to assess the role of each drug alone or in combination in the suppression of Ki-67. Ki-67 was centrally assessed. Treatment allocation was performed by computer-generated random permuted blocks and stratified by geographic location—United Kingdom versus North America (United States and Canada; Data Supplement). Letrozole 2.5 mg/d was administered orally continually and palbociclib 125 mg/d was administered orally on a 21-days-on, 7-days-off schedule. Protocol-specified dose modifications for palbociclib were recommended for various adverse events.

### Procedures

After randomization, patients visited the clinic each week for the first 4 weeks, then every other week until week 14. Follow-up visits were at 30 days post-trial treatment and 12 months after random assignment. Assessments required at these visits are described in the protocol.

Core-cut biopsies and trial-specific blood samples were taken at baseline (post–random assignment), 2 weeks (before commencement of second drug for groups B and C), and 14 weeks or at the discontinuation of study therapy (within 48 hours of the last dose of trial treatment).

### Outcomes

Principal outcome analyses focused on changes between baseline and the end of treatment (EoT) and compared letrozole (A) with palbociclib plus letrozole (B + C + D). Coprimary end points were clinical response (ultrasound; Eastern Cooperative Oncology Group[17]) and (ii) change in the proliferation marker Ki-67 (immunohistochemistry). Secondary end points included pCR, changes in surgical intent, and safety. In addition, changes in Ki-67 between baseline and week 2 and week 2 to EoT were compared in groups for which treatment differed during each respective time period. Prespecified exploratory biomarkers included cleaved poly (ADP-ribose) polymerase (c-PARP; apoptosis).

### Statistical Analysis

The PALLET trial was powered (90%) using a conventional comparative design with alpha ($\alpha$ = 5% overall) split between the two coprimary end points. Improved clinical

response would be detected for palbociclib plus letrozole over letrozole (complete response: 31% *v* 21%; partial response: 57% *v* 54%; stable disease: 5% *v* 15%; progressive disease: 2% *v* 5%) with 284 patients ($\alpha$ = 4% and 90% power). With a 5% nonevaluable rate and 3:2:2:2 allocation, the recruitment target was 306 patients. Improvement with decreased Ki-67 from 80% in group A to 90% in groups B plus C plus D (log-fold change of −0.693; standard deviation of 1.5) would be detected with 279 patients with $\alpha$ = 1% and 90% power. Interim analyses were planned at 25% and 50% of trial end point information, and the trial would have been terminated for futility at the second analysis if there was no evidence that either end point favored palbociclib.

Post hoc analysis revealed that there were 279 evaluable clinical responses (93:186), which under the initial sample size specifications would give 88.1% power. Log-fold changes in Ki-67 were available for 190 patients (61.9%; 65:125) to provide 75% power.

All patients were analyzed according to the intention to treat approach. Clinical response was treated as an ordinal outcome and compared using the Mann-Whitney test in all patients with Eastern Cooperative Oncology Group response data available at EoT. Changes in Ki-67 and c-PARP were analyzed on the natural log-fold scale in patients with biopsy data available at both baseline and EoT. As an exploratory analysis, complete cell cycle arrest (CCCA) at EoT (defined as Ki-67 of 2.7% or less) was compared between groups using a logistic regression model that adjusted for recruitment region and histologic type.

## RESULTS

Between February 27, 2015, and March 8, 2018, 307 women were recruited—166 from the United Kingdom (Data Supplement) and 141 from North America (Data Supplement; group A, n = 103; group B, n = 68; group C, n = 69; group D, n = 67; Fig 1). Baseline demographic and clinical characteristics were similar across treatment groups (Table 1).

Overall, 253 patients (82.4%) completed 14 weeks of treatment. In the letrozole group (A) this was 85% (n = 88) compared with 81% (n = 165) of patients who received palbociclib plus letrozole (B + C + D). The median percentage of scheduled letrozole received was 99% in all treatment groups. The median [interquartile range (IQR)] percentages of the scheduled dose of palbociclib received in groups B, C, and D were 99.2% (82.9% to 100.0%), 90.9% (67.8% to 100.0%), and 97.4% (79.2% to 100.0%), respectively. Palbociclib was interrupted/delayed in 21.6% of patients (n = 44), dose was reduced in 2.0% of patients (n = 4), and treatment was interrupted/delayed and dose reduced in 15.2% of patients (n = 31; Data Supplement).

Clinical response outcomes at EoT were available for 279 patients (90.8%; Table 2). In the letrozole group (A), 46

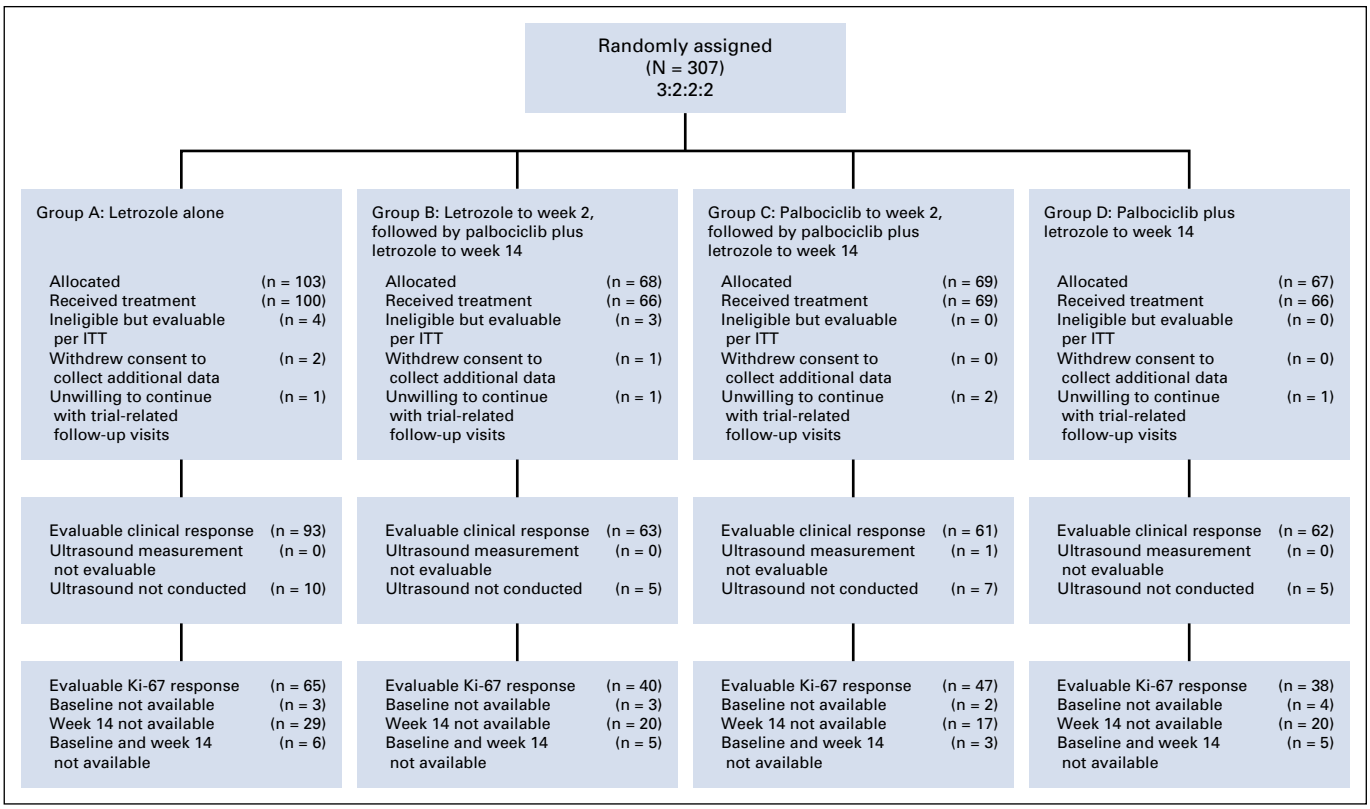


**FIG 1.** CONSORT diagram. ITT, intention to treat.

**TABLE 1.** Baseline Demographic and Clinical Characteristics by Randomized Treatment Group

| Characteristic | Letrozole Alone | Letrozole + Palbociclib From Week 2 | Palbociclib + Letrozole From Week 2 | Palbociclib + Letrozole | Palbociclib + Letrozole Regimen |
|---|---|---|---|---|---|
| | Group A (n = 103) | Group B (n = 68) | Group C (n = 69) | Group D (n = 67) | Groups B, C and D (n = 204) |
| Median age, years (IQR) | 65.8 (59.4-72.0) | 66.3 (60.4-72.5) | 63.5 (59.3-70.5) | 63.8 (58.5-69.1) | 64.4 (59.5-71.1) |
| Recruitment region | | | | | |
| United Kingdom | 56 (42.4) | 37 (54.4) | 37 (53.6) | 36 (53.7) | 110 (53.9) |
| North America | 47 (45.6) | 31 (45.6) | 32 (46.4) | 31 (46.3) | 94 (46.1) |
| Tumor grade | | | | | |
| Low | 13 (12.6) | 6 (8.8) | 4 (5.8) | 9 (13.4) | 19 (9.3) |
| Intermediate | 70 (68.0) | 54 (79.4) | 52 (75.4) | 51 (76.1) | 157 (77.0) |
| High | 19 (18.5) | 7 (10.3) | 13 (18.8) | 7 (10.5) | 27 (13.2) |
| Not known | 1 (1.0) | 1 (1.5) | 0 (0.0) | 0 (0.0) | 1 (0.5) |
| Histologic type | | | | | |
| Ductal | 74 (71.8) | 49 (72.1) | 46 (66.7) | 45 (67.2) | 140 (68.7) |
| Lobular | 24 (23.3) | 14 (20.6) | 19 (27.5) | 18 (26.9) | 51 (25.0) |
| Mixed ductal and lobular | 4 (3.9) | 1 (1.5) | 4 (5.8) | 2 (3.0) | 7 (3.4) |
| Mucinous | 1 (1.0) | 4 (5.9) | 0 (0.0) | 2 (3.0) | 6 (2.9) |
| ER status | | | | | |
| Positive | 103 (100.0) | 68 (100.0) | 69 (100.0) | 67 (100.0) | 204 (100.0) |
| PgR status | | | | | |
| Positive | 74 (71.8) | 47 (69.1) | 41 (59.4) | 53 (79.1) | 141 (69.1) |
| Negative | 15 (14.6) | 10 (14.7) | 15 (21.7) | 7 (10.5) | 32 (15.7) |
| Not determined | 14 (13.7) | 11 (16.2) | 13 (18.8) | 7 (10.5) | 31 (15.2) |
| Surgical intent at baseline | | | | | |
| Partial mastectomy/ lumpectomy | 61 (59.2) | 45 (66.2) | 40 (58.0) | 39 (58.2) | 124 (60.8) |
| Total or modified radical mastectomy | 39 (37.9) | 20 (29.4) | 25 (36.2) | 24 (35.8) | 69 (33.8) |
| Missing | 3 (2.9) | 3 (4.4) | 4 (5.8) | 4 (6.0) | 11 (5.4) |

NOTE. Data are presented as No. (%) unless otherwise noted. See the Data Supplement (Results) for information on the associations between baseline characteristics and the availability of Ki-67 results.

Abbreviations: ER, estrogen receptor; IQR, interquartile range; PgR, progesterone receptor.

(49.5%) of 93 patients achieved a complete or partial response compared with 101 (54.4%) of 186 patients with palbociclib plus letrozole (B + C + D). There was no evidence that the inclusion of palbociclib changed clinical response as measured by ultrasound ($P = .20$).

Log-fold changes in Ki-67 were available for 190 patients (61.9%; Fig 2 and Table 2). Reasons for nonavailability of paired Ki-67 results included missing and unevaluable samples (Data Supplement) with histologic type and geographical region the only baseline characteristics differentiating availability. Median log-fold change in Ki-67 between baseline and EoT was −2.2 (IQR, −3.4 to −1.0) in the letrozole group (A) compared with −4.1 (IQR, −5.0 to −2.8; one-sided $P < .001$) in palbociclib plus letrozole groups (B + C + D). This corresponds to a geometric mean change of −88.5% (95% CI, −92.3% to −82.9%) compared with −97.4% (95% CI, −98.1% to −96.4%). The geometric mean ratio was 0.16 (95% CI, 0.13 to 0.18; $P < .001$). CCCA was observed in 38 (58.5%) of 65 patients in the letrozole group (A) compared with 113 (90.4%) of 125 in palbociclib plus letrozole groups (B + C + D; odds ratio, 6.83; 95% CI, 3.12 to 14.98; $P < .001$).

Between baseline and week 2 there was a median log-fold change in Ki-67 with letrozole alone (A + B) of −1.3 (IQR, −2.9 to −0.7) compared with −3.1 (IQR, −4.1 to −1.5) in palbociclib alone (C; $P < .001$). Median log-fold change in Ki-67 at week 2 with palbociclib plus letrozole (D) was −3.9 (IQR, −4.7 to −2.7; $P < .001$) compared with groups who received letrozole alone for the first 2 weeks (A+B), and there was no significant difference between

**TABLE 2.** End Point by Randomized Treatment Group

| Variable | Letrozole Alone | | | Letrozole + Palbociclib From Week 2 | | | Palbociclib + Letrozole From Week 2 | | | Palbociclib + Letrozole | | | Palbociclib + Letrozole Regimen | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Group A (n = 93) | | | Group B (n = 63) | | | Group C (n = 61) | | | Group D (n = 62) | | | Groups B, C, and D (n = 186) | | |
| Clinical response, No. (%) | | | | | | | | | | | | | | | |
| Complete response | 2 (2.2) | | | 1 (1.6) | | | 2 (3.3) | | | 1 (1.6) | | | 4 (2.2) | | |
| Partial response | 44 (47.3) | | | 30 (47.6) | | | 33 (54.1) | | | 34 (54.8) | | | 97 (52.2) | | |
| Stable disease | 42 (45.2) | | | 30 (47.6) | | | 25 (41.0) | | | 24 (38.7) | | | 79 (42.5) | | |
| Progressive disease | 5 (5.4) | | | 2 (3.2) | | | 1 (1.6) | | | 3 (4.8) | | | 6 (3.2) | | |
| | Group A (n = 87) | | | Group B (n = 60) | | | Group C (n = 60) | | | Group D (n = 60) | | | Groups B, C, and D (n = 180) | | |
| Pathologic complete response, No. (%) | | | | | | | | | | | | | | | |
| pCR breast (any nodal status) | 1 (1.1) | | | 1 (1.7) | | | 3 (5.0) | | | 2 (3.3) | | | 6 (3.3) | | |
| pCR breast and nodes | 0 (0.0) | | | 1 (1.7) | | | 1 (1.7) | | | 0 (0.0) | | | 2 (1.1) | | |
| | Group A | | | Group B | | | Group C | | | Group D | | | Groups B, C and D | | |
| | No. | Med | IQR | No. | Med | IQR | No. | Med | IQR | No. | Med | IQR | No. | Med | IQR |
| Log-fold change in Ki-67 | | | | | | | | | | | | | | | |
| From baseline to week 14 | 65 | −2.2 | −3.4 to −1.0 | 40 | −4.1 | −5.1 to −2.7 | 47 | −4.0 | −5.1 to −3.0 | 38 | −3.9 | −5.0 to −2.9 | 125 | −4.1 | −5.0 to −2.8 |
| From baseline to week 2 | 61 | −1.3 | −2.8 to −0.6 | 39 | −1.3 | −2.5 to −0.8 | 44 | −3.1 | −4.1 to −1.5 | 32 | −3.9 | −4.7 to −2.7 | 115 | −2.8 | −4.1 to −1.2 |
| From week 2 to week 14 | 61 | −0.1 | −1.1 to 0.4 | 39 | −2.1 | −3.5 to −1.3 | 44 | −0.4 | −2.1 to 0.0 | 32 | 0.0 | −0.1 to 0.9 | 115 | −1.0 | −2.2 to 0.0 |
| Log-fold change in c-PARP | | | | | | | | | | | | | | | |
| From baseline to week 14 | 47 | −0.4 | −1.0 to 0.2 | 34 | −0.9 | −1.4 to −0.5 | 37 | −0.8 | −1.4 to −0.2 | 28 | −0.6 | −1.3 to −0.2 | 99 | −0.8 | −1.4 to −0.3 |
| From baseline to week 2 | 42 | −0.1 | −0.5 to −0.3 | 31 | −0.3 | −0.7 to −0.1 | 36 | −0.3 | −0.8 to −0.2 | 23 | −0.5 | −0.7 to 0.0 | 90 | −0.4 | −0.7 to −0.1 |
| From week 2 to week 14 | 42 | −0.3 | −0.8 to 0.0 | 31 | −0.6 | −1.2 to −0.3 | 36 | −0.3 | −0.8 to 0.1 | 23 | −0.3 | −0.7 to 0.1 | 90 | −0.4 | −0.9 to 0.0 |

Abbreviations: c-PARP, cleaved poly (ADP-ribose) polymerase; IQR, interquartile range; Med, median; pCR, pathologic complete response.

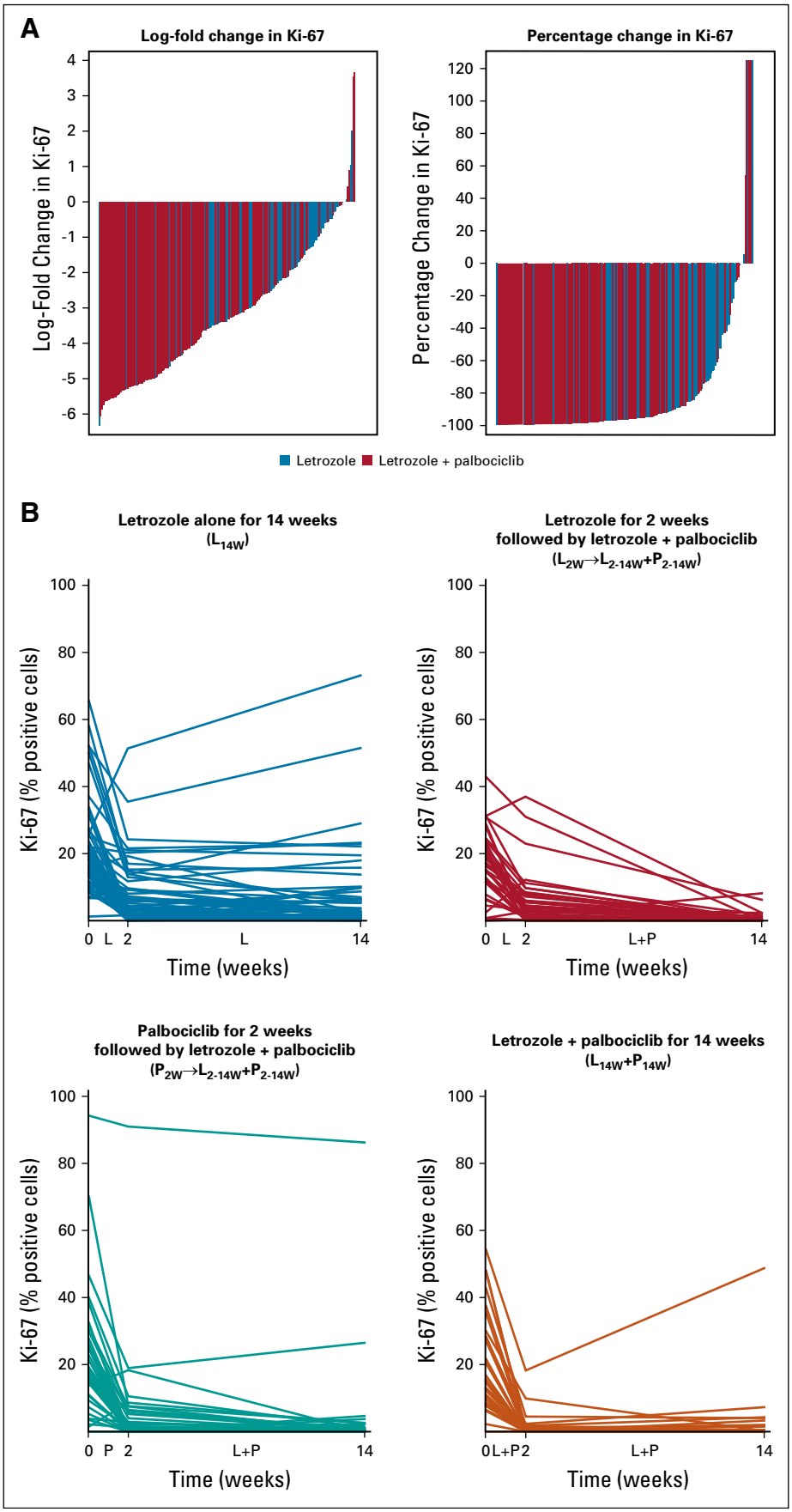


**FIG 2.** (A) Waterfall plot of log-fold change and percentage change in Ki-67 between baseline and the end of treatment. Five patients had a percentage increase greater than 125%. (B) Spaghetti plots of individual trajectories of Ki-67 by randomized treatment group.

palbociclib alone (C) and palbociclib plus letrozole (D; $P$ = .06). At week 2, CCCA was more common with palbociclib plus letrozole than with palbociclib alone [D: 47 (89%) of 53 patients; 95% CI, 76% to 96% *v* C: 44 (72%) of 61 patients; 95% CI, 59% to 82%; $P$ = .04]. Between week 2 and week 14, there was a median log-fold change in Ki-67 of −0.1 (IQR, −1.1 to 0.4) with letrozole alone (A) compared with −2.1 (IQR, −3.5 to −1.3; $P$ < .001), −0.4 (IQR, −2.1 to 0.0; $P$ = .12), and 0.0 (IQR, −0.1 to 0.9; $P$ = .08) in groups B, C, and D, respectively.

pCR in the breast occurred infrequently and there was no evidence of a difference between letrozole [A; one (1.1%) of 87 patients; 95% CI, 0.0 to 6.2) compared with palbociclib plus letrozole [B + C + D; six (3.3%) of 180 patients; 95% CI, 1.2% to 7.1%; $P$ = .43). pCR in breast, axillary lymph nodes, and nonaxillary sentinel nodes were found in two (1.1%) of 180 patients (95% CI, 0.0% to 4.0%; $P$ = 1.00) who received palbociclib plus letrozole (B + C + D). There was no difference in the proportion of patients whose intended surgery changed from mastectomy at baseline to breast conservation at week 14 with letrozole [A; 13 (14.1%) of 92 patients; 95% CI: 7.7% to 23.0%] compared with palbociclib plus letrozole [B + C + D; 25 (14.1%) of 177 patients; 95% CI, 9.4% to 20.1%; $P$ = 1.00].

Apoptosis, as measured by c-PARP, was a prespecified exploratory biomarker with paired data available for 146 patients ((47.6%; Fig 3 and Table 2). Other prespecified exploratory biomarkers are under analysis but not yet available to report. The log-fold change in c-PARP between baseline and EoT was −0.42 (IQR, −0.99 to 0.20) with letrozole (A) compared with −0.80 (IQR, −1.35 to −0.29; one-sided $P$ < .001) with palbociclib plus letrozole (B + C + D). Post hoc analyses found that at week 2 there was a median log-fold change in c-PARP with letrozole (A + B) of −0.1 (IQR, −0.6 to 0.2) compared with −0.3 (IQR, −0.8 to −0.1) with palbociclib (C; $P$ = .004). Median log-fold change in c-PARP at week 2 with palbociclib plus letrozole (D) was −0.5 (IQR, −0.7 to 0.0) compared with letrozole (A + B; $P$ = .07), and there was no evidence of a difference between palbociclib (C) versus palbociclib plus letrozole (D; $P$ = .47). Between week 2 and week 14, there was a median log-fold change in c-PARP of −0.3 (IQR, −0.7 to 0.0) with letrozole (A) compared with −0.6 (IQR, −1.2 to −0.3; $P$ = .09), −0.3 (IQR, −1.0 to 0.1; $P$ = .72), and −0.3 (IQR, −0.7 to 0.1; $P$ = .82) in groups B, C, and D, respectively. Any-grade adverse event (AE), irrespective of the relationship to the study treatment, was reported in 91% of patients with letrozole (A) and 99% of patients with palbociclib plus letrozole (B + C + D). The majority of AEs were grade 1 or 2 (91%). Grade 3 or greater AEs were reported in 17% of patients with letrozole (A) and in 50% of those in palbociclib plus letrozole groups (B + C + D; $P$ < .001; Table 3). In total, eight patients in palbociclib plus letrozole groups (B + C + D) experienced 10 grade 4 or 5 AEs. Of these, one patient experienced a grade 5 acute respiratory distress syndrome which was considered to be unrelated to letrozole or palbociclib.

## DISCUSSION

PALLET is the largest randomized trial of a CDK4/6 inhibitor in the neoadjuvant setting and demonstrates that the addition of palbociclib to letrozole markedly enhanced the suppression of malignant cell proliferation as assessed by Ki-67. In addition, there was a significant increase in the number of patients who achieved CCCA in their tumor after 14 weeks of combination therapy compared with letrozole alone (90% *v* 59%). Although the suppression of Ki-67 in the first 2 weeks by palbociclib alone was significantly greater than by letrozole alone, the combination palbociclib plus letrozole enhanced the proportion of patients who achieved CCCA. In terms of toxicity, PALLET detected no new signals with the addition of palbociclib in patients with early-stage primary BC.

The lack of difference in clinical response rate (54.3% *v* 49.5%) is perhaps not a surprise given the cytostatic nature of endocrine-based therapies in contrast to similar neoadjuvant trials using cytotoxic chemotherapies in triple-negative BC or targeted combinations in HER2-positive BC.[18] In slower growing ER-positive tumors, therapies with a predominantly antiproliferative effect will yield a slower reduction in tumor size,[19] especially over a short timeframe of 14 weeks. When using primary endocrine therapy to downstage ER-positive BC, maximal tumor shrinkage may take at least 9 to 12 months.[20] We also demonstrate for the first time to our knowledge—using c-PARP expression as a biomarker—that unlike chemotherapy, wherein apoptosis increases in addition to an antiproliferative effect,[21] CDK4/6 therapy in combination with an AI produces a greater suppression—not an increase—in apoptosis compared with endocrine therapy alone. Measurement of c-PARP is only one of a number of approaches to assessing apoptosis in situ. It is notable that the decrease observed in the AI alone arm of PALLET is similar to that observed when using the terminal deoxynucleotidyl transferase dUTP nick end labeling method in the IMPACT trial.[22] This reduction in cell death could also explain why overall tumor volume—that is, clinical response—as determined by ultrasound did not substantially change, nor did the surgical breast conservation rate, despite the markedly enhanced antiproliferative effect. Indeed, these data are consistent with the PALOMA-2 study (ClinicalTrials.gov identifier: NCT01740427) in advanced BC in which the greatest clinical impact was observed in progression-free survival (hazard ratio, 0.58), rather than the best objective response rate (ORR; 55% *v* 44%).[6,8] Similarly, ORR with abemaciclib plus AI in the MONARCH-3 trial was 59% versus 44% with AI alone,[23] and with ribociclib plus AI in the MONALEESA-2 trial ORR was 52.7% versus 37.1% with AI alone,[24] yet both studies also had highly significant improvements in

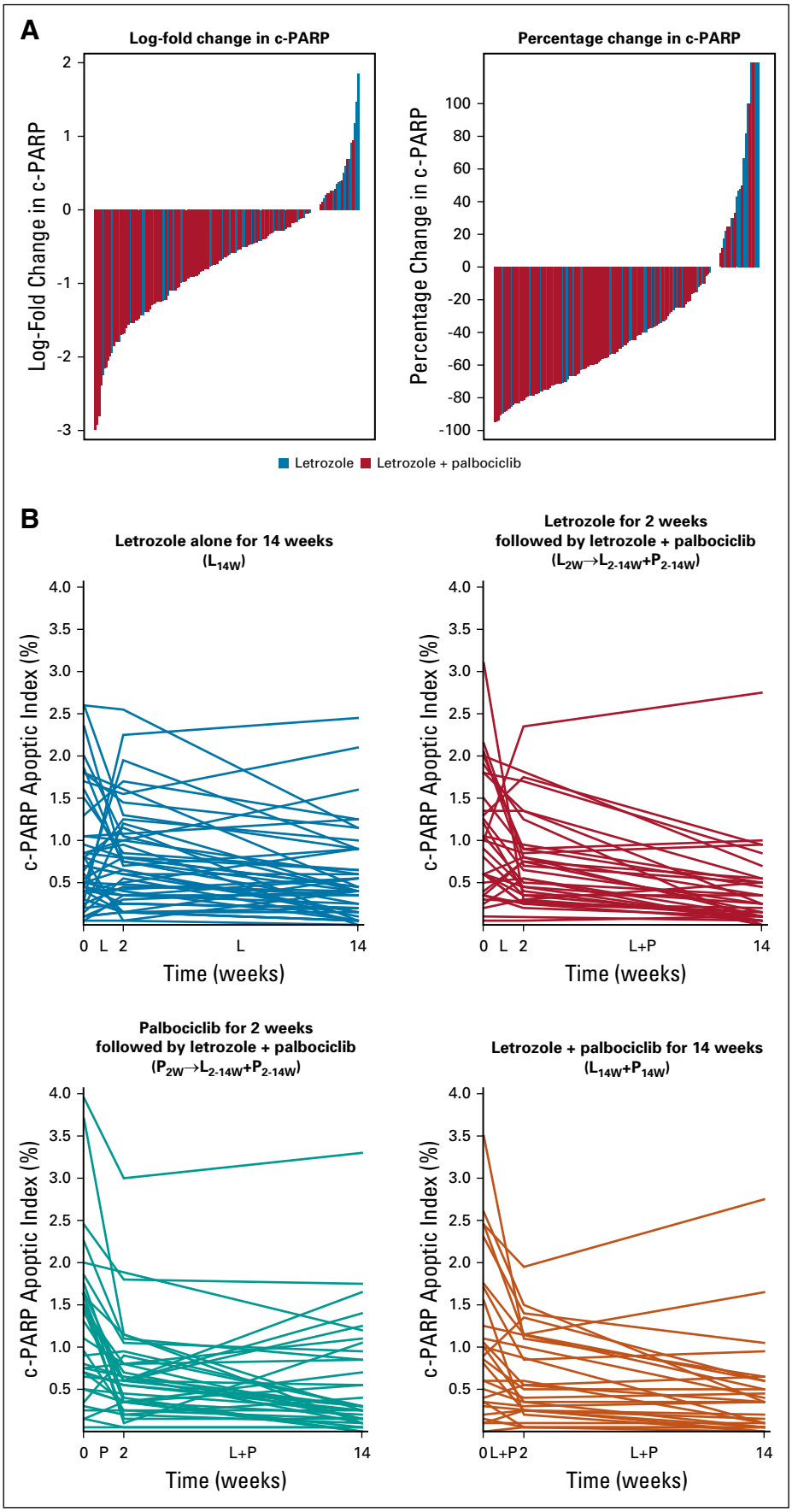


**FIG 3.** (A) Waterfall plot of log-fold change and percentage change in cleaved poly (ADP-ribose) polymerase (c-PARP) between baseline and the end of treatment. Five patients had a percentage increase greater than 125%. (B) Spaghetti plots of individual trajectories of c-PARP by randomized treatment group.

**TABLE 3.** Most Frequently Occurring Adverse Events

| | Letrozole Alone | | Palbociclib + Letrozole Regimen | |
|---|---|---|---|---|
| | Group A (n = 100) | | Groups B + C + D (n = 201) | |
| MedDRA-Coded AE Preferred Term | Any Grade | Grade ≥ 3 | Any Grade | Grade ≥ 3 |
| Fatigue | 41 (41.0) | 0 (0.0) | 117 (58.2) | 4 (2.0) |
| Neutrophil count decreased | 2 (2.0) | 0 (0.0) | 110 (54.7) | 82 (40.8) |
| Hot flush | 40 (40.0) | 0 (0.0) | 54 (26.9) | 0 (0.0) |
| Nausea | 18 (18.0) | 0 (0.0) | 50 (24.9) | 0 (0.0) |
| Arthralgia | 26 (26.0) | 0 (0.0) | 37 (18.4) | 1 (0.5) |
| Headache | 21 (21.0) | 0 (0.0) | 37 (18.4) | 0 (0.0) |
| WBC count decreased | 1 (1.0) | 0 (0.0) | 49 (24.4) | 12 (6.0) |
| Diarrhea | 14 (14.0) | 1 (1.0) | 33 (16.4) | 2 (1.0) |
| Constipation | 10 (10.0) | 0 (0.0) | 26 (12.9) | 0 (0.0) |
| Breast pain | 12 (12.0) | 0 (0.0) | 20 (10.0) | 1 (0.5) |
| Platelet count decreased | 0 (0.0) | 0 (0.0) | 31 (15.4) | 0 (0.0) |
| Dizziness | 7 (7.0) | 0 (0.0) | 24 (11.9) | 0 (0.0) |
| Alanine aminotransferase increased | 7 (7.0) | 0 (0.0) | 23 (11.4) | 8 (4.0) |
| Alopecia | 3 (3.0) | 0 (0.0) | 26 (12.9) | 0 (0.0) |
| Hypertension | 11 (11.0) | 8 (8.0) | 15 (7.5) | 9 (4.5) |
| Cough | 3 (3.0) | 0 (0.0) | 21 (10.4) | 0 (0.0) |
| Anemia | 3 (3.0) | 0 (0.0) | 20 (10.0) | 0 (0.0) |
| Epistaxis | 2 (2.0) | 0 (0.0) | 20 (10.0) | 0 (0.0) |
| Stomatitis | 0 (0.0) | 0 (0.0) | 20 (10.0) | 2 (1.0) |
| Depression | 10 (10.0) | 0 (0.0) | 9 (4.5) | 0 (0.0) |
| Pain in extremity | 10 (10.0) | 1 (1.0) | 9 (4.5) | 0 (0.0) |
| Myalgia | 11 (11.0) | 0 (0.0) | 8 (4.0) | 0 (0.0) |

NOTE. Data are presented as No. (%). Data are the number of patients experiencing any-grade or grade 3 or greater AEs as per MedDRA-preferred term AEs. Sorted by most frequent AE of any grade occurring overall. Only AEs occurring in more than 10% of patients in group A or in the palbociclib plus letrozole groups are reported. Percentages within group are based on the as-treated populations.

Abbreviation: AE, adverse event.

progression-free survival (hazard ratio, 0.54 and 0.57, respectively). In early BC, it remains to be seen whether the antiproliferative differences observed in the PALLET trial, despite the lack of change in ORR in the neoadjuvant setting, will translate into an effect on time to recurrence in ongoing adjuvant studies.

Previous studies of neoadjuvant endocrine therapy have also demonstrated that suppression of Ki-67, rather than clinical response, is a better indicator of therapeutic activity in ER-positive early BC. In the IMPACT trial, no difference in clinical response rate was observed between anastrozole, tamoxifen, or the combination (37% *v* 36% *v* 39%)[25] after 3 months of therapy in 330 patients. However, significantly greater suppression of Ki-67 was reported for anastrozole compared with tamoxifen at 12 weeks (81.6% *v* 61.9%).[13,26] These differences in Ki-67 suppression were paralleled by the greater benefit from anastrozole versus tamoxifen or the combination of anastrozole and tamoxifen in the ATAC trial.[27] Furthermore, the log-fold reduction in Ki-67 in IMPACT was a predictor of subsequent RFS in the adjuvant setting.[13] Similarly, the greater suppression of Ki-67 by letrozole than tamoxifen in P024[28] paralleled the greater improvement in RFS with letrozole in the analogous BIG1-98 adjuvant trial (ClinicalTrials.gov identifier: NCT00004205).[29] When the different AIs were compared in Z1031 (ClinicalTrials.gov identifier: NCT00265759),[14] the lack of difference in Ki-67 suppression was supported by similar RFS between groups in the adjuvant studies MA-27 (ClinicalTrials.gov identifier: NCT00066573)[30] and FACE (ClinicalTrials.gov identifier: NCT00248170).[31] More recently, the large United Kingdom POETIC trial (ClinicalTrials.gov identifier: NCT02338310) confirmed that the lack of suppression of Ki-67 after 2 weeks of preoperative AI predicted for a significantly worse 5-year RFS.[32] CDK4/6 inhibitors restrict passage through the cell cycle and, like endocrine agents, are therefore antiproliferative. However, whether the lack of Ki-67 suppression after neoadjuvant

CDK4/6 inhibitor therapy is similarly predictive remains unconfirmed.

Suppression of Ki-67 in the first 2 weeks by palbociclib alone was significantly greater than that by letrozole alone, a finding also reported recently in the small, phase II preoperative palbociclib trial (ClinicalTrials.gov identifier: NCT02008734).[33] However, in the PALLET trial, the four-group design demonstrated that the palbociclib plus letrozole combination enhanced the proportion of patients who achieved CCCA in the first 2 weeks, and that the addition of the AI maximizes Ki-67 suppression.

In a previous small, phase II study (NeoPalAna; ClinicalTrials.gov identifier: NCT01723774) in 50 patients with ER-positive early BC of different intrinsic subtypes, sequential biopsies were taken in patients who were initiated on anastrozole for 4 weeks, followed by the addition of palbociclib to study the additional change or decrease in Ki-67.[34] Rates of CCCA with palbociclib and anastrozole were significantly higher (87%) than with anastrozole alone (26%), and biomarker analysis suggested that response to palbociclib occurred independently of tumor grade, absence of progesterone receptor expression, or mutation in *p53*, *PIK3CA,* or *PTEN* genes, but was correlated with RB1 mutation status. Extensive gene and protein expression analyses are being undertaken in PALLET as exploratory end points. These will be correlated with antiproliferative response and could yield important information about predictive biomarkers for this class of therapy in the early BC setting, which can be tested in the adjuvant setting.

In NeoPalAna, it was reported that the antiproliferative effect of palbociclib diminished rapidly after treatment stopped in some patients, which suggests the need for continued therapy.[34] For this reason, in PALLET, we aimed to ensure that the 14-week biopsy was taken during exposure to drug therapy and excluded 2.6% of 14-week samples as they fell outside the 48-hour window since the last drug dose taken. In addition, 13.0% of patients had an unevaluable sample which could reflect minimal cellularity in the core biopsy. Studies to assess the correlation between the 14-week samples with cellularity and Ki-67 in the excised surgical sample are ongoing.

In the only other randomized neoadjuvant trial of CDK4/6 inhibitors in ER-positive early BC (NeoMONARCH; ClinicalTrials.gov identifier: NCT02441946), 224 patients were randomly assigned to either anastrozole, abemaciclib (Verzenio; Eli Lilly, Indianapolis, IN), or the combination, with biopsies taken at baseline, 2 weeks, and after 16 weeks of therapy.[35] Combination abemaciclib plus anastrozole was associated with a greater geometric mean decrease in Ki-67 at 2 weeks (−92.6% *v* −63.2%), with a significant increase in CCCA (66% *v* 14%). To date, biomarkers of response or resistance to abemaciclib have not been identified, although reports of induced histologic changes that are suggestive of tumor differentiation and increased lymphocytic infiltration were observed in some cases.[35]

The incomplete availability of biopsy samples could potentially bias the biologic findings for Ki-67 and c-PARP. When EoT biopsies were not taken (n = 38), this often occurred with incomplete treatment (n = 29; 76%). Excluding these cases could overstate the proportion who responded; however, there were an approximately equal number of cases in which Ki-67 was unevaluable as a result of scant tumor in the biopsy. A similar level of Ki-67 suppression would be expected in these cases compared with the evaluable population and so would not be expected to bias our findings. Other trials that featured Ki-67 as an end point have observed similar evaluable proportions. In the NeoMONARCH study, 138 (61.9%) of 223 patients were evaluable for Ki-67 compared with 190 (61.9%) of 307 in our trial. Analyses of Ki-67 and c-PARP levels between baseline and week 2 and from week 2 to EoT in PALLET were conducted post hoc and did not adjust for multiple testing and so should be cautiously interpreted. Nonetheless, such findings match our expectations that the addition of palbociclib to letrozole would increase the suppression of cell proliferation.

In conclusion, the PALLET trial demonstrated that the addition of palbociclib to letrozole markedly enhanced the suppression of malignant cell proliferation as measured by Ki-67 expression, yet did not increase tumor shrinkage as determined by clinical ultrasound. Correlating biomarkers of antiproliferative response in the context of a randomized neoadjuvant study will be important in determining which patients may derive the most benefit from CDK4/6 inhibitors in ongoing adjuvant studies in early BC.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy in Estrogen Receptor–Positive Early Breast Cancer: PALLET Trial**

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**Stock and Other Ownership Interests:** Pfizer
**Honoraria:** Bicycle Therapeutics

**Mitch Dowsett**
**Honoraria:** Myriad Genetics
**Consulting or Advisory Role:** GTx, Radius Health, Orion Pharma
**Research Funding:** Pfizer (Inst), Radius Health (Inst)
**Travel, Accommodations, Expenses:** Pfizer, Myriad Genetics
**Other Relationship:** Institute of Cancer Research

**Judith M. Bliss**
**Research Funding:** AstraZeneca (Inst), Merck Sharp & Dohme (Inst), Medivation (Inst), Puma Biotechnology (Inst), Clovis Oncology (Inst), Pfizer (Inst), Janssen-Cilag (Inst), Novartis (Inst), Roche (Inst)
**Travel, Accommodations, Expenses:** Pfizer

No other potential conflicts of interest were reported.