Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): a multicentre, open-label, randomised, phase 2 trial

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Summary

Background Endocrine treatment is recommended by clinical guidelines as the preferred treatment option for premenopausal as well as postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer. In real-world clinical practice, however, a substantial number of patients are treated with chemotherapy. We aimed to compare the clinical antitumour activity and safety of palbociclib plus endocrine therapy with that of capecitabine chemotherapy in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer.

Methods This multicentre, open-label, randomised, phase 2 study was done in 14 academic institutions in South Korea. Premenopausal women aged 19 years or older with hormone receptor-positive, HER2-negative breast cancer that had relapsed or progressed during previous tamoxifen therapy and with an Eastern Cooperative Oncology Group performance status of 0–2 were included. One line of previous chemotherapy for metastatic breast cancer was allowed. Patients were randomly assigned, using a random permuted block design (with a block size of two), to receive palbociclib plus combination endocrine therapy (oral exemestane 25 mg per day for 28 days and oral palbociclib 125 mg per day for 21 days every 4 weeks plus leuprolide 3·75 mg subcutaneously every 4 weeks) or chemotherapy (oral capecitabine 1250 mg/m² twice daily for 2 weeks every 3 weeks). Randomisation was stratified by previous chemotherapy for metastatic breast cancer and visceral metastasis. The primary endpoint was progression-free survival. All analyses were done in a modified intention-to-treat population that excluded patients who did not receive study medication. This study is registered with ClinicalTrials.gov, NCT02592746, and is ongoing for follow-up of overall survival.

Findings Between June 15, 2016, and Dec 10, 2018, 189 patients were enrolled, of whom 184 were randomly assigned to the palbociclib plus endocrine therapy group (n=92) or the capecitabine group (n=92). Six patients in the capecitabine group withdrew from the study before drug administration; therefore, 92 patients in the palbociclib plus endocrine therapy group and 86 patients in the capecitabine group were included in the modified intention-to-treat analyses. 46 (50%) of 92 patients in the palbociclib plus endocrine therapy group and 45 (51%) of 92 in the capecitabine group were treatment naive for metastatic breast cancer. During a median follow-up of 17 months (IQR 9–22), median progression-free survival was 20·1 months (95% CI 14·2–21·8) in the palbociclib plus endocrine therapy group versus 14·4 months (12·1–17·0) in the capecitabine group (hazard ratio 0·659 [95% CI 0·437–0·994], one-sided log-rank p=0·0235). Treatment-related grade 3 or worse neutropenia was more common in the palbociclib plus endocrine therapy group than in the capecitabine group (69 [75%] of 92 *vs* 14 [16%] of 86 patients). 2 (2%) patients in the palbociclib plus endocrine therapy group and 15 (17%) patients in the capecitabine group had treatment-related serious adverse events. No treatment-related deaths occurred.

Interpretation Exemestane plus palbociclib with ovarian function suppression showed clinical benefit compared with capecitabine in terms of improved progression-free survival in premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer. Palbociclib plus exemestane with ovarian suppression is an active treatment option in premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer who have been pretreated with tamoxifen.

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Research in context

Evidence before this study

We searched PubMed for research articles published in English between Jan 1, 1999, and July 31, 2019, on clinical trials assessing the role of CDK4/6 inhibitors in the treatment of women with hormone receptor-positive, HER2-negative metastatic breast cancer. The search terms used were "HR-positive" and "CDK4/6 inhibitors" and "breast cancer". We also examined relevant treatment guidelines (eg, US National Comprehensive Cancer Network, European Society for Medical Oncology, and St Gallen guidelines) and published congress abstracts (eg, from the European Society for Medical Oncology annual meeting, the National Comprehensive Cancer Network annual conference, and the St Gallen international breast cancer conference). The published literature recommended endocrine therapy as the preferred standard treatment for patients with hormone receptor-positive, HER2-negative metastatic breast cancer irrespective of their menopausal status. However, the debate about chemotherapy versus endocrine therapy for patients with hormone receptor-positive metastatic breast cancer is ongoing, especially for those with a higher tumour burden and those with disease recurrence within 24 months of adjuvant endocrine therapy. Furthermore, in real-world clinical practice, 24–43% of patients with hormone receptor-positive, HER2-negative metastatic breast cancer in the USA and Europe were initially started on chemotherapy treatment before CDK4/6 inhibitors were approved by the US Food and Drug Administration. Several trials have shown that in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer, treatment with a CDK4/6 inhibitor plus endocrine therapy with ovarian function suppression with a gonadotropin-releasing hormone agonist produced significantly longer progression-free survival than did endocrine therapy alone (MONALEESA-7 and subpopulations of PALOMA-3 and MONARCH-2). However, whether a combination of endocrine therapy plus a CDK4/6 inhibitor is more effective than chemotherapy for young premenopausal patients remains unknown, and there are still insufficient data about the effects of CDK4/6 inhibitors in premenopausal women.

Added value of this study

To our knowledge, this study is the first to compare treatment with the CDK4/6 inhibitor palbociclib plus endocrine therapy with single-agent capecitabine chemotherapy exclusively in premenopausal women. Our study showed that palbociclib plus exemestane with ovarian function suppression (with leuprolide) led to significantly longer median progression-free survival compared with capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer. The median progression-free survival in the palbociclib plus endocrine group in our study was intermediate between those reported for the PALOMA-3 and MONALEESA-7 trials, although indirect cross-trial treatment comparisons must be interpreted with caution. Considering that most (86%) of the study population had tamoxifen-resistant disease at study enrolment, this is a remarkable improvement. Most of the patients who received tamoxifen as a component of their adjuvant endocrine therapy had disease recurrence during adjuvant therapy or within 12 months after completion or discontinuation of the therapy, which differs to the findings of other studies of first-line CDK4/6 inhibitor treatment, such as PALOMA-2 and MONALEESA-2. In these studies, most populations had endocrine-sensitive relapse, in which their disease had recurred 12 months after completion of adjuvant endocrine therapy (with disease-free survival of at least 6 years).

Implications of all the available evidence

Palbociclib plus exemestane with ovarian function suppression is an active treatment option in tamoxifen-pretreated premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer who are candidates for cytotoxic chemotherapy. Combination endocrine therapy with CDK4/6 inhibitors could change practice in establishing endocrine therapy as a standard therapy for premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer.

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Introduction

Clinical guidelines[1] recommend endocrine treatment as the standard treatment of choice for patients with hormone receptor-positive, HER2-negative metastatic breast cancer, irrespective of their menopausal status. However, in real-world practice, 24–43% of patients with hormone receptor-positive, HER2-negative metastatic breast cancer in the USA and Europe were initially started on chemotherapy before CDK4/6 inhibitors were approved by the US Food and Drug Administration (March, 2017).[2–6] Chemotherapy use was even more common in patients aged younger than 50 years than in older patients.[3] In Asian countries, including South Korea, treatment patterns differ: for premenopausal women, availability of endocrine therapies apart from tamoxifen and gonadotropin-releasing hormone (GnRH) agonists is limited because fulvestrant and aromatase inhibitors are only approved for postmenopausal women, and the use of these agents with a GnRH agonist was not reimbursed by insurance at the time of our trial. Thus, contrary to almost all guidelines, premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer have been more likely to receive chemotherapy than endocrine therapy.[7,8] In postmenopausal patients, the initial and subsequent use of chemotherapy is often based on the endocrine resistance of the tumour and physicians' choice based on the toxicity profile of chemotherapeutic agents. Physicians' concern about the poor prognosis associated with aggressive intrinsic tumour behaviour might also affect the choice of

chemotherapy for younger patients, as might the different biology of breast cancer in women of different ethnicities.[9,10] Thus, an unmet medical need exists for clinical trials in premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer, who are often under-represented in such studies.[11–13]

Several trials have shown that in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer, a CDK4/6 inhibitor plus endocrine therapy with ovarian function suppression with a GnRH agonist resulted in significantly longer progression-free survival than did endocrine therapy alone (in MONALEESA-7[14] and in subpopulations of the PALOMA-3[15] and MONARCH-2[16] studies). Furthermore, the first demonstration of a significant overall survival benefit for a CDK4/6 inhibitor plus endocrine therapy as first-line treatment was from the phase 3 MONALEESA-7 trial,[17] which evaluated ribociclib plus endocrine therapy exclusively in perimenopausal and premenopausal women with hormone receptor-positive, HER2-negative disease. However, whether combination CDK4/6 inhibitor plus endocrine therapy is more effective than chemotherapy for premenopausal patients remains unknown, and data about the effects of CDK4/6 inhibitors in premenopausal women are still scarce.[14] Capecitabine is one of the most popular chemotherapy options for HER2-negative metastatic breast cancer,[12,14] with prospective studies having demonstrated its favourable efficacy and safety profiles.[18–20] Capecitabine combined with docetaxel is indicated for patients in whom anthracycline-containing chemotherapy has failed, and capecitabine as monotherapy is indicated for patients in whom taxanes and anthracycline-containing chemotherapy have failed, or for whom further anthracycline-containing therapy is not indicated.[1] In clinical practice, capecitabine is often used as the first chemotherapeutic agent in patients with hormone receptor-positive, HER2-negative breast cancer that has progressed during endocrine therapy.

On the basis of this information, we postulated that premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer would achieve a superior progression-free survival with the CDK4/6 inhibitor palbociclib combined with endocrine treatment than with capecitabine chemotherapy. We aimed to evaluate the safety and clinical antitumour activity of exemestane plus a GnRH agonist combined with palbociclib compared with that of capecitabine in premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer.

Methods

Study design and participants

The KCSG-BR15-10 trial was a multicentre, open-label, randomised, controlled, phase 2 trial done in 14 academic institutions in South Korea (appendix p 3).

For the **protocol** see https://sites.google.com/site/youngpearlkcsg

See **Online** for appendix

Premenopausal women aged 19 years or older with histologically confirmed, hormone receptor-positive, HER2-negative metastatic or recurrent breast cancer were eligible. Hormone receptor status and HER2 status were confirmed locally by immunohistochemistry or by fluorescence or silver in-situ hybridisation. Premenopausal status was defined as having had the most recent menstrual period within the past 12 months in any patients (irrespective of previous treatment received); for patients on tamoxifen, a period within the previous 3 months, a plasma oestradiol concentration higher than 10 pg/mL, follicle-stimulating hormone (FSH) concentration of at least 40 IU/L, or plasma oestradiol and FSH concentrations within the laboratory-defined premenopausal range; or in patients with chemotherapy-induced amenorrhoea, a plasma oestradiol concentration higher than 10 pg/mL, FSH concentration of at least 40 IU/L, or plasma oestradiol and FSH concentrations within the laboratory-defined premenopausal range. Eligible patients must have had disease progression based on Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) after previous tamoxifen treatment, with disease progression defined as progression during therapy for metastatic disease or progression during or after completion or discontinuation of adjuvant endocrine therapy with tamoxifen, regardless of the treatment-free interval. Patients who had received one previous line of endocrine treatment or one previous line of chemotherapy in the context of advanced disease were eligible. Patients who had received radiotherapy to less than 25% of their bone marrow and had recovered from the acute toxic effects of the treatment were also eligible. Additional inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate bone marrow, renal, and liver function; and the absence of other concurrent or previous malignant neoplasms, with the exceptions of adequately controlled in-situ uterine carcinoma or cutaneous basal cell carcinoma.

Exclusion criteria were postmenopausal status; previous treatment with an aromatase inhibitor, CDK4/6 inhibitors including palbociclib, or capecitabine; symptomatic or asymptomatic brain parenchymal or leptomeningeal metastases; symptomatic serious visceral metastases needing urgent treatment; and other severe medical conditions such as serious uncontrolled intercurrent infections and serious intercurrent medical or psychiatric illness (see appendix pp 4–5 for full list of inclusion and exclusion criteria).

The study was done in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki, and was approved by the institutional ethics committees of each hospital and the Korean Cancer Study Group institutional review board. Written informed consent was obtained from each participant. The current study protocol is available online.

Randomisation and masking

Patients were randomly assigned (1:1) to either the palbociclib plus endocrine therapy group or the

capecitabine group. The random permuted block method with a block size of two was used for randomisation. Randomisation was stratified by previous chemotherapy for metastasis (yes or no) and the presence or absence of visceral metastasis. To mask group assignment during the randomisation process, a random allocation sequence in each stratum was generated by an independent statistician and stored in the electronic case report form. Participants were assigned to the treatment group according to assignment group in the electronic case report form. However, patients and clinicians were not masked during the trial because of the different administration schedules of the two study regimens. Thus, this was an open-label trial in which outcome assessment and data analysis were not blinded.

Procedures

Treatment for patients in the palbociclib plus endocrine therapy group comprised oral palbociclib 125 mg once daily for 3 weeks plus oral exemestane 25 mg once daily for 4 weeks and leuprolide 3·75 mg subcutaneously every 4 weeks until progression or unacceptable toxicity. Treatment for patients in the capecitabine group comprised oral capecitabine 1250 mg/m² twice a day for 2 weeks, repeated every 3 weeks until progression or unacceptable toxicity. Palbociclib dose modifications were as follows: a new cycle of treatment was started only when the absolute neutrophil count was at least $1{\cdot}0\times10^9$ cells per L, the platelet count was at least 100×10^9 per L, and all non-haematological toxicities other than alopecia were a maximum of grade 2 severity, as defined by the US National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 4.03. A cycle of palbociclib could be delayed for up to 3 weeks to allow sufficient time for recovery. If the treatment could not be re-started after a 3-week delay, the patients were removed from the study, but follow-up for progression-free survival after discontinuation of the treatment was continued. Palbociclib treatment was interrupted or delayed for patients with the following adverse events: grade 3–4 anaemia, grade 3–4 neutropenia, grade 3 or worse non-haematological toxicities, grade 3 corrected QT interval prolongation, and grade 3 or worse hepatotoxicity. Dose reductions of palbociclib by one dose level (to 100 mg per day) and, if needed, by two dose levels (to 75 mg per day) were allowed depending on the type and severity of toxicity encountered. Patients requiring more than two dose level reductions were discontinued from palbociclib treatment and continued with exemestane plus leuprolide in the active treatment phase. Once a dose had been reduced for a particular patient, all subsequent cycles were administered at that reduced dose level, unless a further dose reduction was required. No dose escalations were permitted in this study. No specific dose adjustments were recommended for grade 1–2 treatment-related toxicity. However, the investigators managed their patients according to their medical judgment based on the particular clinical circumstances. The start of a new cycle of palbociclib was delayed until the severity of an adverse event decreased to grade 2 or better. Dose modifications, delays, or interruptions were not permitted for exemestane or leuprolide.

Capecitabine doses were modified as follows. First, at the development of grade 2 toxicities, administration of planned medication was interrupted until these resolved to grade 0–1, then continued at the same dose. Second, for grade 3 toxicities, treatment was interrupted until these resolved to grade 0–1, then continued at 75% of the starting dose (first occurrence) or 50% of the starting dose (second occurrence). Any grade 4 toxicities in the capecitabine group prohibited the patient from continuing the study.

All patients underwent a prestudy clinical evaluation, which included a physical examination; measurement of vital signs with the ECOG performance status; chest X-ray; CT scans of the chest, abdomen, and pelvis; and a bone scan. Blood chemistry results and complete blood counts were obtained for every treatment cycle. For the first 12 weeks, radiological tumour measurement and evaluation by CT were done every 6 weeks, and then follow-up evaluations were done every 8 weeks until disease progression. Disease response was assessed by the investigators, according to RECIST, version 1.1.[21,22] Toxicity was assessed on the first day of each treatment cycle using the NCI-CTC, version 4.03.

Outcomes

The primary endpoint of this study was investigator-assessed progression-free survival, which was calculated from the date of randomisation to the documented date of disease progression or death or the last visit date. Secondary endpoints were overall survival, quality of life, toxicity, the proportion of patients with objective responses, the proportion of patients with clinical benefit, and exploration of biomarkers. Overall survival was measured from the date of randomisation to the date of death from any cause, with censoring at the last visit date. Objective responses were defined as complete or partial responses according to RECIST, version 1.1. Clinical benefit was defined as either an objective response, or the best overall response of complete or partial response or stable disease together with a progression-free survival of 24 weeks or longer. Disease control (the proportion of patients with disease control) was a post-hoc exploratory endpoint and was defined as a complete or partial response or stable disease. Patient-reported outcomes and correlative biomarker analyses are not reported in this paper and will be reported separately.

Statistical analysis

Our hypothesis was that the median progression-free survival would be longer in the palbociclib plus endocrine therapy group than in the capecitabine group, with an expected median progression-free survival of 8 months in the palbociclib plus endocrine therapy group versus 5 months in the capecitabine group, yielding a hazard ratio

(HR) of 0·625. To test this hypothesis with a one-sided significance level of α=0·05 and 80% power, the target number of patients for enrolment was 126. We planned an interim analysis at 76 progression events and the final analysis at 152 progression events. By use of the O'Brien and Fleming's spending function, we defined one-sided α levels of 0·0055 and 0·0485 for the interim and final analyses. However, the plan had to be changed to no interim analysis because of the high accrual rate on Sept 27, 2018. In 2017, in view of the high annual enrolment recruitment and after discussion among investigators and funders about the costs of drug supplies to extend statistical power, a protocol amendment (protocol version 5.0; July 5, 2017) increased the target sample size to 172 patients. Assuming an approximately 5% attrition because of ineligibility or dropout, we needed to recruit 182 patients into the trial.

We did all analyses of efficacy and safety in a modified intention-to-treat population that included all patients who underwent randomisation but excluded those who did not receive any study medication. We estimated progression-free survival using the Kaplan–Meier method and compared progression-free survival between groups using the log-rank test. We tested the proportional hazards assumption on the basis of Schoenfeld residuals (appendix p 1). Subgroup analyses and the analysis of overall response, disease control, and clinical benefit in patients with measurable disease at baseline, and time to the best response were post hoc. We analysed overall survival using the Kaplan-Meier method, and we compared objective responses and clinical benefit between the groups using the χ^2 test or Fisher's exact test. Patients who had not had any progression event at the time of data analysis were censored at the last date they were known to be progression free. Patients with no tumour assessments after baseline were censored at the date of randomisation. Patients who were not reported as having died at the time of the analysis were censored using the date they were last known to be alive. Two-sided p values are presented for all analyses except for progression-free survival for which we present one-sided p values. Statistical analyses were done with SAS, version 9.4.

This study is registered with ClinicalTrials.gov, NCT02592746.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

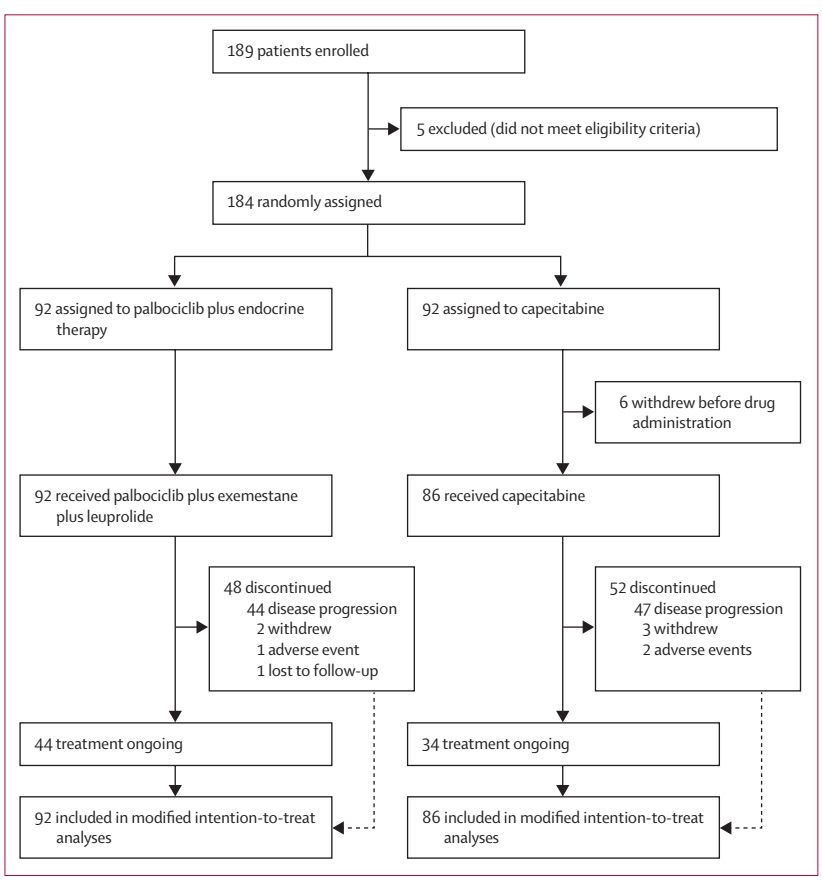

Figure 1: **Trial profile**

Results

Between June 15, 2016, and Dec 10, 2018, 189 patients were enrolled. Of these patients, five who failed the screening procedure were excluded, and 184 patients were randomly assigned to either palbociclib plus exemestane plus leuprolide (palbocliclib plus endocrine therapy; n=92) or capecitabine (n=92; figure 1). Six patients in the capecitabine group withdrew from the study before drug administration. Consequently, 178 patients (92 in the palbociclib plus endocrine therapy group and 86 in the capecitabine group) were included in the final efficacy and safety analyses. At a median follow-up duration of 17 months (IQR 9–22), the database was locked on Feb 1, 2019, and the final analyses were performed.

The baseline characteristics of the patients in the modified intention-to-treat population were well balanced between groups (table 1). The median age of both groups was 44 years (IQR 40–48). 46 (50%) patients in the palbociclib plus endocrine therapy group and 45 (51%) patients in the capecitabine group were receiving first-line treatment for metastatic disease. Among the 124 patients with recurrence, 58 (90%) of 64 patients in the palbociclib plus endocrine therapy group and 50 (83%) of 60 patients in the capecitabine group had received adjuvant chemotherapy. Of these 124 patients who had recurrent disease from curative surgery, 17 (14%) patients had a tamoxifen-sensitive recurrence. Most of the patients in both groups who had recurrent disease had received adjuvant endocrine therapy with tamoxifen with or without a GnRH agonist.

Median progression-free survival from randomisation was 20·1 months (95% CI 14·2–21·8) in the palbociclib plus endocrine therapy group compared with 14·4 months (12·1–17·0) in the capecitabine group (HR 0·659 [95% CI 0·437–0·994]; p=0·0235; figure 2). 44 patients in the palbociclib plus endocrine therapy group and 47 patients in the capecitabine group had disease progression or had died at the time of data cutoff on Feb 1, 2019 (appendix p 9). The median overall survival for all patients was not reached (data not shown): at the time of the data cutoff, 12 patients (seven in the palbociclib plus endocrine therapy group and five in the capecitabine group) had died. All 12 patients died of cancer progression (appendix p 2).

In a post-hoc subgroup analysis, the improvement in progression-free survival in the palbociclib plus endocrine therapy group was observed in patients aged older than 35 years, in patients with worse ECOG performance status, those who had not previously received chemotherapy in a metastatic setting, and in patients with non-visceral disease (figure 3). However, progression-free survival did not differ significantly between the treatment groups in subgroups according to number of previous lines of treatment for metastatic breast cancer, objective responses, and number of metastatic sites (figure 3).

34 (37%) of 92 patients in the palbocliclib group and 29 (34%) of 86 in the capecitabine group achieved an objective response, and 89 (97%) patients in the palbociclib plus endocrine therapy group and 78 (91%) patients in the capecitabine group achieved disease control. The proportion of patients with clinical benefit did not differ signficicantly between the groups (table 2). Among 178 patients, 119 (67%) patients had target lesions (measurable disease) at baseline (61 in the palbociclib and endocrine therapy group and 58 in the capecitabine group). A post-hoc analysis of overall responses, disease control, and clinical benefit in these patients is in table 2. A post-hoc analysis showed that the time to the best response did not differ significantly between groups in these 119 patients with measurable disease, with a median of 4·3 months (95% CI 3·0–5·6) in the palbociclib plus endocrine therapy group and 2·9 months (2·6–4·3) in the capecitabine group (p=0·111 by log-rank test).

At data cutoff, 44 patients in the palbociclib plus endocrine therapy group and 34 patients in the capecitabine group remained on treatment. The median dose intensity of palbociclib was 510·8 mg per week (IQR 459·6–579·4; 78% of the expected dose) in the palbociclib plus endocrine therapy group and 10 272·2 mg/m² per week (9204·3–11 666·7; 88% of the expected dose;) in the capecitabine group. Dosing interruptions because of adverse events were required in 88 (96%) patients in the palbociclib plus endocrine therapy group and 65 (76%) patients in the capecitabine group, and dose reductions were required in 44 (48%) patients in the palbociclib plus endocrine therapy group and in 41 (48%) patients in the capecitabine group. The most common reasons for dose interruptions and reductions were neutropenia in the palbociclib plus endocrine therapy group (80 [87%]) and hand-foot syndrome in the capecitabine group (35 [29%]; see

	Palbociclib plus endocrine therapy group (n=92)	Capecitabine group (n=86)
Age, years	44 (40–48)	44 (40–48)
Body-mass index, kg/m²	22 (21–25)	22 (21–25)
Hormone receptor status		
Oestrogen receptor positive and progesterone receptor positive	70 (76%)	64 (74%)
Oestrogen receptor positive and progesterone receptor negative	22 (24%)	22 (26%)
Eastern Cooperative Oncology Group performance status		
0	54 (59%)	48 (56%)
1–2	38 (41%)	38 (44%)
Metastatic sites		
Bone only	22 (24%)	18 (21%)
Visceral organs	45 (49%)	43 (50%)
Lung	29 (32%)	22 (26%)
Liver	17 (18%)	19 (22%)
Number of metastatic organs		
1	50 (60%)	38 (53%)
≥2	42 (40%)	48 (47%)
Disease-free survival from the first diagnosis of stage I–III breast cancer		
<24 months	12 (13%)	15 (17%)
≥24 months	52 (57%)	45 (52%)
De-novo stage IV disease	28 (30%)	26 (30%)
Tamoxifen resistance (including recurrence within 12 months after completion of adjuvant tamoxifen)		
Yes	76 (83%)	77 (90%)
No	16 (17%)	9 (10%)
Previous cytotoxic chemotherapy for metastatic breast cancer		
Yes	22 (24%)	18 (21%)
No	70 (76%)	68 (79%)
Previous lines of treatment for metastatic breast cancer		
0	46 (50%)	45 (51%)
1	30 (33%)	30 (52%)
2	16 (17%)	11 (13%)
Previous (neo)adjuvant treatment		
Cytotoxic chemotherapy	58/64 (90%)	50/60 (83%)
Anthracycline based	16/64 (25%)	11/60 (18%)
Anthracycline and taxane based	40/64 (63%)	36/60 (60%)
Others	2/64 (3%)	3/60 (5%)
Endocrine treatment	60/64 (94%)	55/60 (92%)
Tamoxifen	43/64 (67%)	47/60 (78%)
Tamoxifen plus gonadotropin-releasing hormone agonist	17/64 (27%)	8/60 (13%)

Data are median (IQR), n (%), or n/N (%). Percentages might not sum to 100% because of rounding.

Table 1: **Baseline characteristics**

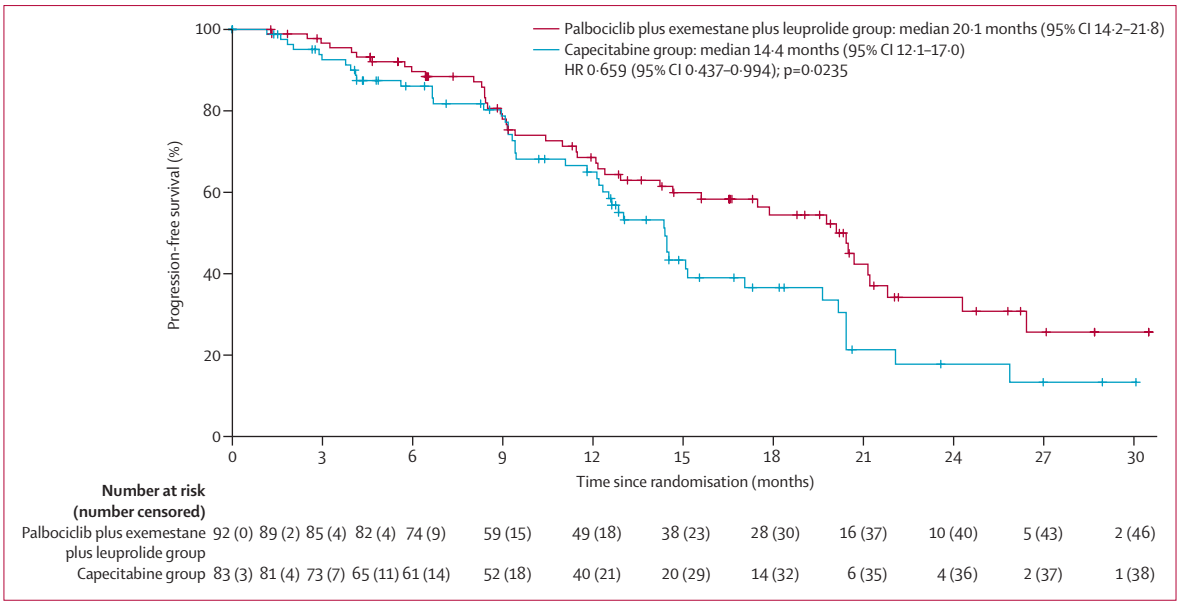

Figure 2: **Progression-free survival curve in the modified intention-to-treat population**
HR=hazard ratio.

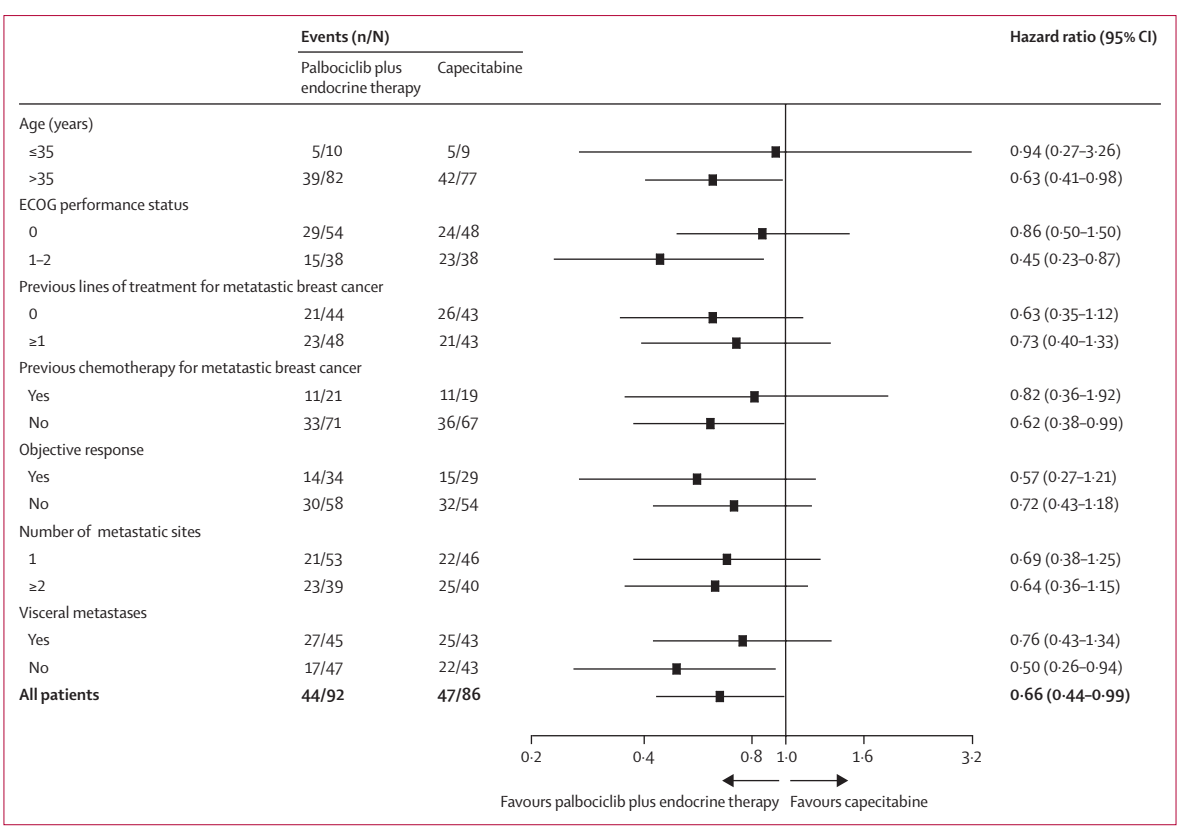

Figure 3: **Forest plot of the post-hoc subgroup analysis**
ECOG=Eastern Cooperative Oncology Group.

appendix p 6 for the full list of reasons). No patient discontinued palbociclib and continued with exemestane plus leuprolide. 48 patients in the palbociclib plus endocrine therapy group and 52 patients in the capecitabine group discontinued the study drugs (appendix p 9).

Haematological toxicity of all grades was observed more frequently in the palbociclib plus endocrine therapy group than in the capecitabine group, the most common of which were neutropenia (74 [80%] *vs* 32 [37%]) and leukopenia (46 [50%] *vs* ten [12%]; table 3). The proportion of patients with treatment-related grade 3 or worse neutropenia was higher in the palbociclib plus endocrine therapy group than in the capecitabine group (69 [75%] of 92 *vs* 14 [16%] of 86). Non-haematological toxicities of grade 3 or worse were rarely observed in either group (table 3). 2 (2%) patients in the palbociclib plus endocrine therapy group and 15 (17%) patients in the capecitabine group had treatment-related serious adverse events. No treatment-related deaths occurred.

	Palbociclib plus endocrine therapy group (n=92)	Capecitabine group (n=86)	p value
Objective responses	34 (37%)	29 (34%)	0·781
Objective responses in patients with target lesions	31/61 (51%)	26/58 (45%)	0·387
Disease control	89 (97%)	78 (91%)	0·480
Disease control in patients with target lesions	58/61 (95%)	51/58 (88%)	0·262
Clinical benefit	74 (80%)	58 (67%)	0·105
Clinical benefit in patients with target lesions	48/61 (79%)	38/58 (66%)	0·134

Data are n (%) or n/N (%) unless otherwise stated.

Table 2: **Summary of secondary efficacy endpoints**

	Palbociclib plus endocrine therapy group (n=92)			Capecitabine group (n=86)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	2 (2%)	46 (50%)	13 (14%)	15 (17%)	14 (16%)	0
Febrile neutropenia	0	3 (3%)	0	0	1 (1%)	0
Leukopenia	36 (39%)	10 (11%)	0	10 (12%)	0	0
Anaemia	3 (3%)	4 (4%)	0	4 (5%)	2 (2%)	0
Thrombocytopenia	0	1 (1%)	1 (1%)	0	0	0
Arthralgia	20 (22%)	0	0	5 (6%)	0	0
Headache	21 (23%)	0	0	8 (9%)	0	0
Fatigue	26 (28%)	0	0	17 (20%)	0	0
Mucositis	35 (38%)	1 (1%)	0	16 (19%)	3 (3%)	0
Nausea	11 (12%)	0	0	29 (34%)	1 (1%)	0
Diarrhoea	11 (12%)	1 (1%)	0	36 (39%)	0	0
Hand–foot syndrome	1 (1%)	0	NE	74 (86%)	12 (14%)	NE

Haematological and non-haematological toxic effects in this table were reported by patients. No treatment-related deaths occurred. See appendix (pp 7–8) for all adverse events (irrespective of relationship to treatment). NE=not evaluable.

Table 3: **Treatment-related adverse events (per patient) in the safety analysis**

Discussion

Palbociclib plus exemestane with ovarian suppression with leuprolide prolonged progression-free survival compared with capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer. This trial was designed to compare combination endocrine treatment with single-agent chemotherapy in premenopausal women who had disease progression or relapse during or after previous endocrine therapy with tamoxifen. In premenopausal women with hormone receptor-positive, HER2-negative breast cancer, chemotherapy is often the preferred treatment option[7] and optimal strategies for endocrine-based therapies remain an important challenge for several reasons, including under-representation of this population in clinical trials and issues regarding optimal ovarian function suppression.[23] In conjunction with our study, an overall survival benefit from combination endocrine treatment with ribociclib demonstrated in MONALEESA-7[17] has provided an insightful rationale for the treatment of patients with premenopausal hormone receptor-positive, HER2-negative metastatic breast cancers. Although PALOMA-3[15] and MONARCH-2[16] showed similar results in terms of progression-free survival, they did not focus exclusively on the premenopausal population and their results in these patients represent a subgroup analysis.[23]

The median progression-free survival of 20·1 months in the palbociclib plus endocrine therapy group is significantly longer than that for those receiving capecitabine (14·4 months) in our study, especially considering the tumour characteristics in our study population. Notably, only a small proportion (14%) of patients had a tamoxifen-sensitive recurrence of disease; most patients (86%) with recurrent disease had a tamoxifen-resistant disease at study enrolment. Most of the patients who received tamoxifen as a component of their adjuvant endocrine therapy had disease recurrence during adjuvant therapy or within 12 months after completion or discontinuation of the therapy. This finding differs from those of other studies of first-line CDK4/6 inhibitor treatment, such as PALOMA-2[24] and MONALEESA-2,[25] in which patients who relapsed during or within 12 months after the end of adjuvant endocrine were excluded; thus, the majority of the patients included in those studies had an endocrine-sensitive relapse. However, our inclusion criteria reflected real-world premenopausal populations of patients who could benefit more from combination endocrine therapy after tamoxifen failure, making this population more homogeneous than those included in previous studies of premenopausal patients,[15,16] although our participants had not been exposed to aromatase inhibitors. In addition, more than half of the patients in our trial had not received previous chemotherapy for their metastatic disease, and approximately a third of the patients had stage IV disease as their initial diagnosis of breast cancer.

To the best of our knowledge, this study is the first to compare treatment with the CDK4/6 inhibitor palbociclib plus endocrine therapy with single-agent capecitabine chemotherapy exclusively in premenopausal women. Most strikingly, the Kaplan-Meier progression-free survival curves of the two treatment groups began to separate after 1 year, which differs from the findings of other trials comparing endocrine treatment plus add-on CDK4/6 inhibitor therapy versus placebo. The Kaplan-Meier curves in these trials[14–16] showed earlier separations than shown in our current study. At 12 months, both capecitabine and combination endocrine therapy had a profound effect on hormone receptor-positive, HER2-negative metastatic breast cancer. However, the progression-free survival curves of the two groups in our trial seem to indicate that the effect of these drugs on progression-free survival was because of a substantial prolongation of the response. In the first 12 months of the trial, less than 40% of the patients in both groups had disease progression, but after 12 months, the curves showed different angles. This finding implies that, in this setting, capecitabine showed strong effects (giving patients at least 14·4 months of progression-free survival), although not as strong as palbociclib plus endocrine therapy. A recent report showed a similar benefit of capecitabine to that shown in our study, which produced a median progression-free survival of 21·4 months in the subgroup of patients with non-visceral metastasis.[26] Our results are also supported by those of the BOLERO-6 trial,[27] in which capecitabine treatment led to a median progression-free survival of 9·6 months, although in that trial exemestane plus everolimus showed no advantage over capecitabine. This might be the main difference between CDK4/6 inhibitors such as palbociclib and other endocrine-overcoming strategies such as mTOR inhibitors.

We observed no important life-threatening toxicities in either treatment group. The much higher proportion of patients with grade 3 or worse neutropenia seen in the palbociclib plus endocrine therapy group than in the capecitabine group of this study is consistent with the results for Asian populations in PALOMA-2.[28] The worse haematological toxic effects seem to be the reason for the relatively lower median dose intensity of palbociclib than that of capecitabine; however, this reduced dose intensity did not result in a lack of efficacy or worse clinical outcomes in the Asian subpopulation analysis of PALOMA-2 or in the current study.[28]

The debate about chemotherapy versus endocrine therapy for patients with hormone receptor-positive metastatic breast cancer is ongoing, especially for those with a higher tumour burden who have a recurrence of disease within 24 months of adjuvant endocrine therapy, who are in particularly high need of a rapid response to further treatment. In this regard, the shorter time to response for the capecitabine group than the palbociclib plus endocrine therapy group might provide a plausible rationale for the previous choice of chemotherapy as the preferred therapeutic option for premenopausal patients with aggressive hormone receptor-positive metastatic breast cancer. Despite the later response in the palbociclib plus endocrine therapy group, the median progression-free survival was significantly longer than that in the capecitabine group. This paradoxical finding might suggest that the response to palbociclib should be carefully assessed to achieve the best response.

Our post-hoc subgroup analysis indicated that the patients who had not undergone chemotherapy before enrolment and who did not have visceral metastases derived the largest benefits from palbociclib combination endocrine therapy compared with capecitabine. This finding suggests that combination therapy with palbociclib plus endocrine therapy might have a much greater role than capecitabine in these patient populations than in other subgroups. However, this result should be interpreted with caution because of the small number of patients.

This study has several limitations. First, it is a phase 2 study, meaning that it has lower statistical power than phase 3 studies. The use of one-sided type I error of 5% might risk false-positive results; however, we believe that this is acceptable for a randomised phase 2 study. In addition, the trial was open label because of the different administration schedules of the two study regimens, which might introduce potential reporting bias for progression events. Finally, central reviews of pathology and independent assessment of progression-free survival were not available. Further translational studies to elucidate potential biomarkers for palbociclib treatment and analysis of quality of life are warranted.

In conclusion, palbociclib plus exemestane with ovarian function suppression is an active treatment option in tamoxifen-pretreated premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer who are candidates for cytotoxic chemotherapy.

Contributors

YHP developed the idea for the study; designed the study protocol; served as principal investigator of the trial; contributed to patient data collection, data acquisition, data analysis, and interpretation of the data; and wrote the first draft of the manuscript. S-AI, KHJ, JHK, and IHP contributed to the conception and design of the trial, patient data collection and data acquisition, and analysis and interpretation of the data. T-YK, GMK, SYK, KEL, HKA, MHL, H-JK, and HJK contributed to patient data collection and data acquisition, and analysis and interpretation of the data. JIL, S-JK, J-YK, K-HL, JS, S-BK, J-SA, and Y-HI contributed to patient data collection and data acquisition. YHP and HKA provided major writing input, developed the statistical analysis plan, and did the analyses. YHP and S-AI wrote the final report. All authors contributed to revisions of the report.

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Data sharing

Because the study is still ongoing and other secondary endpoints will be analysed at the end of the study, data cannot be shared at this time.

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