Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study

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Summary

Background Palbociclib added to endocrine therapy improves progression-free survival in hormone-receptor-positive, HER2-negative, metastatic breast cancer. The PALLAS trial aimed to investigate whether the addition of 2 years of palbociclib to adjuvant endocrine therapy improves invasive disease-free survival over endocrine therapy alone in patients with hormone-receptor-positive, HER2-negative, early-stage breast cancer.

Methods PALLAS is an ongoing multicentre, open-label, randomised, phase 3 study that enrolled patients at 406 cancer centres in 21 countries worldwide with stage II–III histologically confirmed hormone-receptor-positive, HER2-negative breast cancer, within 12 months of initial diagnosis. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance score of 0 or 1. Patients were randomly assigned (1:1) in permuted blocks of random size (4 or 6), stratified by anatomic stage, previous chemotherapy, age, and geographical region, by use of central telephone-based and web-based interactive response technology, to receive either 2 years of palbociclib (125 mg orally once daily on days 1–21 of a 28-day cycle) with ongoing standard provider or patient-choice adjuvant endocrine therapy (tamoxifen or aromatase inhibitor, with or without concurrent luteinising hormone-releasing hormone agonist), or endocrine therapy alone, without masking. The primary endpoint of the study was invasive disease-free survival in the intention-to-treat population. Safety was assessed in all randomly assigned patients who started palbociclib or endocrine therapy. This report presents results from the second pre-planned interim analysis triggered on Jan 9, 2020, when 67% of the total number of expected invasive disease-free survival events had been observed. The trial is registered with ClinicalTrials.gov (NCT02513394) and EudraCT (2014-005181-30).

Findings Between Sept 1, 2015, and Nov 30, 2018, 5760 patients were randomly assigned to receive palbociclib plus endocrine therapy (n=2883) or endocrine therapy alone (n=2877). At the time of the planned second interim analysis, at a median follow-up of 23·7 months (IQR 16·9–29·2), 170 of 2883 patients assigned to palbociclib plus endocrine therapy and 181 of 2877 assigned to endocrine therapy alone had invasive disease-free survival events. 3-year invasive disease-free survival was 88·2% (95% CI 85·2–90·6) for palbociclib plus endocrine therapy and 88·5% (85·8–90·7) for endocrine therapy alone (hazard ratio 0·93 [95% CI 0·76–1·15]; log-rank p=0·51). As the test statistic comparing invasive disease-free survival between groups crossed the prespecified futility boundary, the independent data monitoring committee recommended discontinuation of palbociclib in patients still receiving palbociclib and endocrine therapy. The most common grade 3–4 adverse events were neutropenia (1742 [61·3%] of 2840 patients on palbociclib and endocrine therapy *vs* 11 [0·3%] of 2903 on endocrine therapy alone), leucopenia (857 [30·2%] *vs* three [0·1%]), and fatigue (60 [2·1%] *vs* ten [0·3%]). Serious adverse events occurred in 351 (12·4%) of 2840 patients on palbociclib plus endocrine therapy versus 220 (7·6%) of 2903 patients on endocrine therapy alone. There were no treatment-related deaths.

Interpretation At the planned second interim analysis, addition of 2 years of adjuvant palbociclib to adjuvant endocrine therapy did not improve invasive disease-free survival compared with adjuvant endocrine therapy alone. On the basis of these findings, this regimen cannot be recommended in the adjuvant setting. Long-term follow-up of the PALLAS population and correlative studies are ongoing.

Funding Pfizer.

Research in context

Evidence before this study

We searched PubMed and oncology congress websites (American Society of Clinical Oncology, San Antonio Breast Cancer Symposium, European Society of Medical Oncology) between Jan 1, 2000, and Sept 1, 2015, to identify clinical trials of CDK4/6 inhibitors in combination with adjuvant endocrine therapy for patients with oestrogen-receptor-positive, HER2-negative early breast cancer, with the search terms "CDK4/6 inhibitor", "palbociclib", "adjuvant endocrine therapy", and "breast cancer", and with no language restrictions. We found no randomised trials published during this period. Multiple previous clinical trials in patients with metastatic oestrogen-receptor-positive, HER2-negative breast cancer have shown that the combination of a CDK4/6 inhibitor and endocrine therapy in either the first-line or pre-treated settings prolongs both progression-free and overall survival. A single-arm, phase 2 study suggested the combination of 2 years of the CDK4/6 inhibitor palbociclib with ongoing standard adjuvant endocrine therapy was feasible and tolerable. Given the benefits of CDK4/6 inhibitors in the metastatic setting, there has been considerable interest in whether use of this class of drugs in the adjuvant setting will improve outcomes for patients with early-stage oestrogen-receptor-positive, HER2-negative breast cancer.

Added value of this study

To our knowledge, the randomised open-label phase 3 PALLAS study is the first and largest study to evaluate the potential efficacy of the CDK4/6 inhibitor palbociclib in the early-stage adjuvant setting. The results of this pre-planned second interim analysis of the PALLAS trial did not show an improvement in invasive disease-free survival with the addition of palbociclib to ongoing adjuvant endocrine therapy in patients with early-stage oestrogen-receptor-positive, HER2-negative breast cancer.

Implications of all the available evidence

Although palbociclib plus endocrine therapy is an efficacious regimen for metastatic oestrogen-receptor-positive, HER2-negative breast cancer, the use of this combination cannot be recommended in the adjuvant setting. Long-term follow-up of the PALLAS patient population and correlative studies are ongoing.

Introduction

Hormone-receptor-positive breast cancer represents the largest subset of this disease, affecting more than 1 million patients annually worldwide.[1] A fundamental component of systemic therapy for hormone-receptor-positive early breast cancer is adjuvant endocrine therapy, which provides substantial benefits by reducing disease recurrence and the risk of death from breast cancer.[2,3] However, despite improvements in adjuvant endocrine therapy, including the use of aromatase inhibitors, extended duration of therapy, and luteinising hormone-releasing hormone (LHRH) agonists in premenopausal patients, considerable risk of recurrence persists over several decades.[4]

Loss of control of the cell cycle is a hallmark of malignancy, including in hormone-receptor-positive breast cancer.[5] A well accepted mechanism associated with cell-cycle progression in hormone-receptor-positive breast cancer is overexpression of cyclin D or other alterations, or both, leading to phosphorylation of the retinoblastoma protein and unregulated passage from the G1 to S phase of the cell cycle. Inhibitors of cyclin dependent kinases 4 and 6 (CDK4/6) result in hypophosphorylation of the retinoblastoma protein and re-establishment of control of the G1/S transition.[6,7]

The combination of a CDK4/6 inhibitor with endocrine therapy has shown antitumour activity by prolonging progression-free survival and overall survival in the first-line and subsequent-line settings of metastatic hormone-receptor-positive, HER2-negative breast cancer, with an acceptable side-effect profile. Currently, three CDK4/6 inhibitors, including palbociclib, are approved for these indications,[8–17] and are considered standard of care in both first-line and pre-treated settings.[18,19] The toxicity profile of palbociclib is well described, and is notable for reversible neutropenia that is typically not associated with serious infections. Aside from the presence of the oestrogen receptor in hormone-receptor-positive breast cancer, there are no currently approved biomarkers for the selection of CDK 4/6 inhibitors.

Based on the broad activity of CDK4/6 inhibitors for treatment of metastatic breast cancer, as well as the need to further reduce the risk of recurrence in the early setting, the phase 3 PALLAS trial was designed to investigate whether the addition of palbociclib to adjuvant endocrine therapy improves outcomes compared with endocrine therapy alone in patients with hormone-receptor-positive, HER2-negative early breast cancer.

Methods

Study design and participants

PALLAS is an international, multicentre, open-label, randomised, phase 3 study investigating the addition of 2 years of palbociclib to standard adjuvant endocrine therapy for patients with hormone-receptor-positive, HER2-negative early breast cancer. The trial was open to accrual at 406 cancer centres in 21 countries: Australia, Austria, Belgium, Canada, Germany, Hungary, Ireland, Israel, Italy, Japan, Mexico, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, the Netherlands, the UK, and the USA (appendix pp 24–37).

Eligible patients had to have a diagnosis of histologically confirmed stage II or III invasive breast cancer (as per American Joint Committee on Cancer [AJCC] Breast

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See **Online** for appendix

Cancer Staging, version 7) that was oestrogen-receptor-positive or progesterone-receptor-positive, or both, and HER2-negative according to institutional guidelines. Oestrogen receptor, progesterone receptor, and HER2 measurements were done locally according to institutional guidelines, in a Clinical Laboratory Improvement Amendments (CLIA)-approved setting in the USA or a certified laboratory in other countries. Patients must have completed definitive breast surgery (as well as adjuvant or neoadjuvant chemotherapy or radiotherapy, or both, if indicated). Standard adjuvant endocrine therapy of provider and patient choice had to be initiated within 12 months of histological diagnosis, and enrolment was within 6 months of initiating adjuvant endocrine therapy. Patients did not have to have received adjuvant or neoadjuvant chemotherapy, but they must have completed therapy and have had sufficient resolution of side-effects at the time of randomisation. Additionally, receipt of a formalin-fixed paraffin-embedded tumour tissue block at a central biorepository was required before randomisation. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, an absolute neutrophil count of 1500 cells per mm³ or greater, a platelet count of 100 000 per mm³ or greater, haemoglobin concentration of 10 g/dL or higher, total serum bilirubin concentration up to the institutional upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase concentrations up to 1·5 times the institutional ULN, and serum creatinine concentration within normal institutional limits. Patients with uncontrolled intercurrent illness were ineligible. Patients provided written informed consent before any study-specific assessments and procedures were done. Full eligibility criteria are summarised in the study protocol (appendix).

The trial was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The research protocol was approved by local or central institutional review boards or ethics committees. The trial was monitored throughout by an international independent data monitoring committee.

Randomisation and masking

Eligible patients were randomly assigned (1:1) in permuted blocks of random size (4 or 6), stratified by anatomic stage (IIA *vs* IIB or III), previous adjuvant or neoadjuvant chemotherapy (yes *vs* no), age (≤50 years *vs* >50 years), and geographical region (North America *vs* Europe *vs* other). Randomisation was done with telephone-based and web-based interactive response technology. Oracle Corporation (Redwood City, CA, USA) designed the interactive response technology and used a randomisation schedule created by PALLAS statistical staff at the Mayo Clinic (Rochester, MN, USA) with SAS software (version 9.4). The interactive response technology allocated a treatment assignment to individual patients when the enrolling study site accessed the system. Enrolment of patients with stage IIA disease was capped at 1000. Patients were randomly assigned to receive 2 years of palbociclib in addition to ongoing standard adjuvant endocrine therapy, or ongoing standard adjuvant endocrine therapy alone. All therapy was administered as open label without masking.

Procedures

Patients randomly assigned to the palbociclib plus endocrine therapy group received palbociclib (supplied by Pfizer) at a starting dose of 125 mg orally once daily, self-administered on an outpatient basis, on days 1–21, followed by 7 days off, in a 28-day cycle for a total duration of 2 years, in addition to standard adjuvant endocrine therapy, self-administered on an outpatient basis according to local requirements and local standard practice, for a duration of at least 5 years. Standard adjuvant provider-choice and patient-choice endocrine therapy could consist of tamoxifen or an aromatase inhibitor (letrozole, anastrolzole, exemestane), with or without an LHRH agonist. Patients randomly assigned to receive endocrine therapy received standard adjuvant endocrine therapy alone for a duration of at least 5 years.

To monitor for adverse events, patients in both groups were evaluated by physical examination and laboratory testing (including haematology and blood chemistry with liver function tests) at least once every 3 months for the first 2 years, followed by every 6 months to year 5, and annually to year 10. No routine systemic imaging was included as part of study procedures; any clinical imaging was symptom-directed, as per international guidelines.[20] Toxicity evaluation was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Palbociclib dosing interruptions or dose modifications were required as per protocol guidelines, with up to two dose reductions being allowed, to 100 mg and 75 mg. Patients requiring more than two dose reductions or more than 4 weeks of dose interruption were required to discontinue palbociclib therapy. Active efforts, including outreach and education, were ongoing throughout the trial to reduce non-protocol-related palbociclib discontinuation. No dose reduction of endocrine therapy was allowed, but dosing interruptions for up to 4 consecutive weeks were allowed. However, participants missing more than 6 cumulative weeks of endocrine therapy (per treatment year) during the treatment phase of the study were removed from the treatment phase. PRO questionnaires (EORTC QLQ-C30, Brief Fatigue Inventory, Brief Pain Inventory, Breast Cancer Prevention Trial Symptom Scales) and drug adherence questionnaires (drug diaries, Morisky Medication Adherence scale, and the McHorney Brief Estimator) to assess patient-reported outcomes and drug diaries to evaluate adherence to oral therapy were routinely collected for the first 3 years on study. In addition to the baseline tumour block, serial blood samples and any

samples at the time of recurrence were collected and centrally stored.

Outcomes

The primary trial endpoint was invasive disease-free survival based on Standardized Definitions for Efficacy End Points (STEEP) criteria,[21] defined as the time from randomisation to the date of the first event: local or regional invasive ipsilateral recurrence, contralateral invasive breast cancer, distant recurrence, second primary invasive cancer of non-breast origin, or death from any cause. Central review was not done for the primary endpoint. For this analysis, surviving patients who were event-free were censored at the date of disease assessment or withdrawal of consent to be followed up, whichever occurred first. Correlative and exploratory endpoints were invasive disease-free survival excluding second primary invasive cancers of non-breast origin, distant recurrence-free survival (defined as the time from randomisation to the date of the first event; distant recurrence or death from any cause), locoregional recurrence-free survival (defined as the time from randomisation to the date of the first event; local/regional invasive ipsilateral recurrence, contralateral invasive breast cancer, or death from any cause), overall survival (defined as the time period between randomisation and death), safety, translational science, adherence, and patient-reported outcomes. Laboratory and clinical correlative analyses, including translational evaluation of patient biospecimens and examination of quality of life and adherence questionnaires, are ongoing pending final analysis of the trial and will be reported elsewhere.

Statistical analysis

The sample size was based on a target hazard ratio (HR) of 0·75 for the palbociclib plus endocrine therapy group over the endocrine therapy alone group, which translates to a 3-year invasive disease-free survival rate of 92·4% in the palbociclib plus endocrine therapy group, assuming an invasive disease-free survival rate of 89·9% in the endocrine therapy alone group, as a clinically relevant level of improvement in invasive disease-free survival. To have 85% power to detect this difference after accounting for interim analyses, the final analysis was planned to occur when 469 invasive disease-free survival events had been observed. The initial sample size was planned to be 4600 patients; however, the sample size was increased on April 4, 2018, in an approved amendment to 5600 on the basis of improved clinical outcomes and lower event rates observed in contemporary clinical trials.[22]

Two interim analyses based on the primary endpoint were planned to monitor for non-binding futility (both interim analyses) and binding superiority (only the second interim analysis) and were scheduled to occur when 33% (first interim analysis) and 67% (second interim analysis) of the total number of invasive disease-free survival events were observed. The second interim

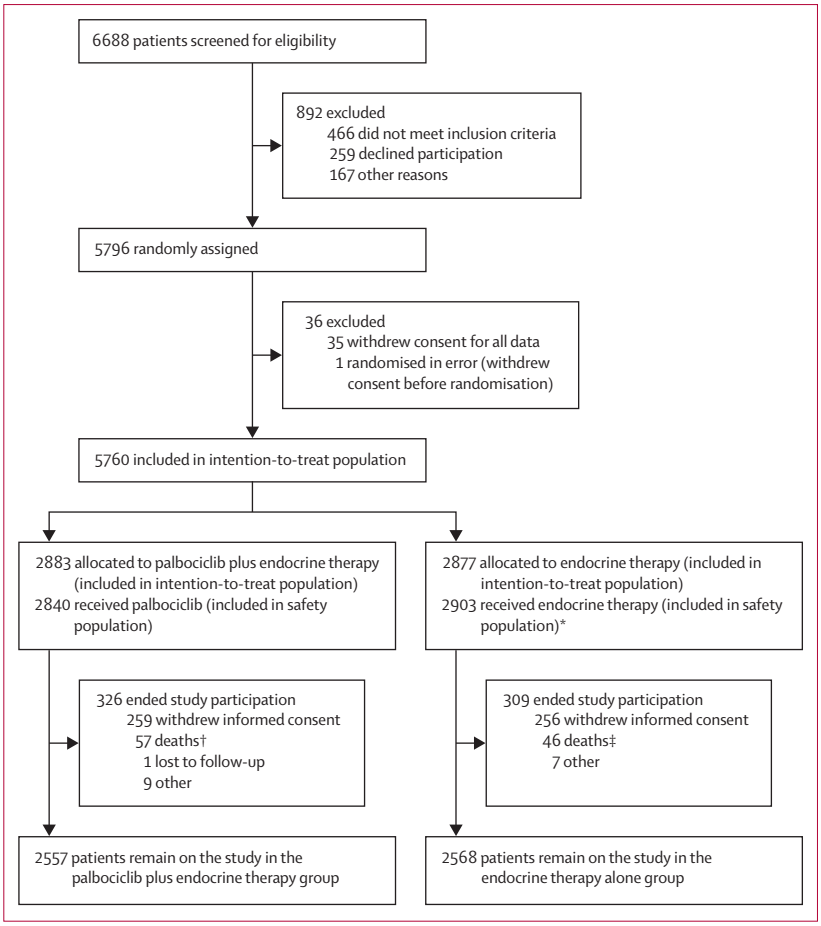

***Figure 1*: Trial profile**

*Includes 37 patients from the palbociclib plus endocrine therapy group who received endocrine therapy only. †Death from any breast cancer (42 [1·5%] of 2883); death from any cause other than breast cancer (nine [0·3%]); death from unknown cause (five [0·2%]); and cause of death pending (one [<0·1%]). ‡Death from any breast cancer (35 [1·2%] of 2877); death from any cause other than breast cancer (eight [0·3%]); and death from unknown cause (three [0·1%]).

	Palbociclib plus endocrine therapy group (n=2883)	Endocrine therapy alone group (n=2877)
Age at randomisation, years	52 (45–61)	52 (45–60)
Age group ≤50 years	1309 (45·4%)	1304 (45·3%)
Sex		
Female (at birth)	2866 (99·4%)	2858 (99·3%)
Male	17 (0·6%)	19 (0·7%)
Menopausal status		
Premenopausal	1552 (53·8%)	1527 (53·1%)
Postmenopausal (including perimenopausal)	1312 (45·5%)	1330 (46·2%)
Not applicable (male patient) or unknown	19 (0·7%)	20 (0·7%)
Race and ethnic group*		
Asian	136 (4·7%)	140 (4·9%)
Black	74 (2·6%)	75 (2·6%)
White	2520 (87·4%)	2495 (86·7%)
Hispanic or Latino	138 (4·8%)	127 (4·4%)
Other or unknown	153 (5·3%)	167 (5·8%)

(Table 1 continues on next page)

	Palbociclib plus endocrine therapy group (n=2883)	Endocrine therapy alone group (n=2877)
(Continued from previous page)		
Geographical region		
Europe	1294 (44·9%)	1297 (45·1%)
North America	1283 (44·5%)	1271 (44·2%)
Other	306 (10·6%)	309 (10·7%)
Disease stage†‡§		
I	8 (0·3%)	9 (0·3%)
IIA	504 (17·5%)	509 (17·7%)
IIB	968 (33·6%)	951 (33·1%)
III	1402 (48·6%)	1408 (48·9%)
T stage†‡		
T0, T1, Tis, or TX	557 (19·3%)	500 (17·4%)
T2	1603 (55·6%)	1636 (56·9%)
T3 or T4	722 (25·0%)	741 (25·8%)
N stage†‡		
N0	367 (12·7%)	383 (13·3%)
N1	1427 (49·5%)	1415 (49·2%)
N2	703 (24·4%)	709 (24·6%)
N3	385 (13·4%)	370 (12·9%)
Histological grade‡		
G1	300 (10·4%)	313 (10·9%)
G2	1622 (56·3%)	1658 (57·6%)
G3	836 (29·0%)	767 (26·7%)
GX	122 (4·2%)	139 (4·8%)
Oestrogen receptor-positive	2872 (99·6%)	2867 (99·7%)
Progesterone receptor-positive	2523 (87·5%)	2555 (88·8%)
Type of surgery		
Mastectomy	1792 (62·2%)	1778 (61·8%)
Breast conservation	1084 (37·6%)	1093 (38·0%)
Combination or unknown	7 (0·2%)	6 (0·2%)
Adjuvant radiotherapy	2558 (88·7%)	2560 (89·0%)
Previous adjuvant or neoadjuvant chemotherapy	2384 (82·7%)	2370 (82·4%)
Initial adjuvant endocrine therapy		
Aromatase inhibitor	1954 (67·8%)	1918 (66·7%)
Tamoxifen	923 (32·0%)	949 (33·0%)
None initiated¶	6 (0·2%)	10 (0·3%)
Concurrent adjuvant LHRH agonist	532 (18·5%)	604 (21·0%)

Data are n (%) or median (IQR). LHRH=luteinising hormone-releasing hormone. *Race and ethnic group were reported by the patient. †Assessed by pathological staging or by clinical staging if pre-operative therapy was given with the higher stage presented in this table. ‡One participant in the palbociclib plus endocrine therapy had unknown stage, T stage, and N stage. Three participants in the palbociclib plus endocrine therapy had unknown histological stage. §Inclusion of stage I patients reflects eligibility violations. ¶Some participants did not initiate protocol-directed therapy, including endocrine therapy.

Table 1: **Baseline characteristics of patients in the intention-to-treat population**

analysis was triggered on Jan 9, 2020, when 67% of the total number of expected invasive disease-free survival events had occurred. To control the overall one-sided type I error rate at 0·025, O'Brien-Fleming type stopping boundaries based on the Lan-DeMets spending function were applied in this group sequential design.

Efficacy analyses were based on the intention-to-treat principle; patients who withdrew consent for the use of all data or before randomisation were excluded from the statistical analysis. The time-to-event efficacy endpoints were compared between randomised groups with stratified log-rank tests, with the stratification factors adjuvant or neoadjuvant chemotherapy (yes *vs* no) and age (≤50 years *vs* >50 years) as recorded at randomisation. The selection of the two stratification factors in the primary analysis was prespecified in the statistical analysis plan and designed to avoid stratification-level subgroups with minimal numbers of invasive disease-free survival events. The distribution of time-to-event efficacy endpoints was summarised with the Kaplan-Meier method according to randomised group, and rates at 1 year, 2 years, and 3 years were estimated with 95% CIs. Finally, HRs with two-sided 95% CIs were estimated with stratified Cox proportional hazards regression models. Unstratified Cox models were also used for the post-hoc comparison of invasive disease-free survival between randomised groups within subgroups on the basis of patient and clinicopathological factors. Proportional hazards assumption was assessed by visually inspecting log(–log(invasive disease-free survival)) versus log(time) within each stratum and Schoenfeld residuals including a locally estimated scatterplot smoothing (LOESS) curve.

The frequency of adverse events was assessed in the safety population (ie, all randomly assigned patients who started palbociclib or endocrine therapy). Patients randomly assigned to the palbociclib group who never received palbociclib, but received endocrine therapy, were included in the endocrine therapy group for safety analyses. Post-hoc competing risk analyses were done to estimate early treatment discontinuations for palbociclib and endocrine therapy among patients initiating therapy for each (the event of interest was early discontinuation; the competing risk was completing treatment per protocol). A post-hoc competing risk analysis was also done to estimate the proportion of patients with at least one dose reduction of palbociclib to 100 mg and 75 mg (the event of interest was first dose reduction to the given level, and the competing risk was discontinuing treatment). To determine whether previous chemotherapy exposure had an impact on the rates of grade 3–4 neutropenia among patients receiving palbociclib and endocrine therapy, the respective rates were compared descriptively in another post-hoc analysis. A post-hoc analysis looking at adverse events of special interest, including interstitial lung disease and venous thromboembolism, was completed. Point estimates and 95% CIs were computed at 6, 12, 18, and 24 months in all competing risk analyses.

Analyses were done with SAS software, version 9.4. Two-sided p values less than 0·05 were considered significant. All data obtained by Jan 9, 2020, triggered by the second interim analysis, were included in the statistical analysis.

This trial is registered with ClinicalTrials.gov (NCT02513394) and EudraCT (2014-005181-30).

Role of the funding source

The PALLAS trial was co-sponsored and led by the academic groups Alliance Foundation Trials and the Austrian Breast and Colorectal Cancer Study Group, in collaboration with PrECOG, the NSABP Foundation, the Breast International Group, the German Breast Group, and in agreement with Pfizer, which provided funding and the drug for the study. The funder collaborated with the co-authors in study design and writing the report. The funder had no role in data collection, data analysis, or data interpretation. All authors had full access to all the data reported in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Sept 1, 2015, and Nov 30, 2018, 5760 patients were randomly assigned to a treatment group and are included in the intention-to-treat population (figure 1). The present analysis included 1013 patients with stage IIA disease enrolled up to Sept 26, 2017. Patient characteristics are shown in table 1. The median age was 52 years (IQR 45–61) and 4729 (82·1%) of 5760 patients had stage IIB or III tumours. 4754 (82·5%) of 5760 patients had received adjuvant or neoadjuvant chemotherapy before randomisation. Adjuvant endocrine therapy selection included 3872 (67·2%) of 5760 patients initiating an aromatase inhibitor, 1872 (32·5%) patients initiating tamoxifen, and 1136 (19·7%) patients receiving a concurrent LHRH agonist. 3382 (58·7%) of 5760 patients had high-clinical-risk disease, described as: four or more nodes involved (>N2), or one to three nodes with either T3 or T4, or grade 3 disease, or both.

At the time of the second interim analysis data cutoff, the observed median duration of palbociclib therapy in patients assigned to receive palbociclib plus endocrine therapy was 18·0 months (IQR 9·2–23·7). At the time of writing this report, 725 (25·5%) of 2840 patients were still receiving palbociclib, 916 (32·3%) had completed planned protocol therapy, and 1199 (42·2%) had discontinued treatment prematurely, with 770 (27·1%) having discontinued treatment due to adverse events. Reasons for palbociclib or endocrine therapy discontinuation are shown in table 2. In a post-hoc analysis, rates of early discontinuation of palbociclib based on competing risk analysis are estimated to be 17·8% (95% CI 16·4–19·3) at 6 months, 29·9% (28·2–31·6) at 12 months, 38·0% (36·2–39·8) at 18 months, and 45·1% (43·1–47·0) at 24 months (appendix p 21). The observed median duration of all adjuvant endocrine therapy at data cutoff was 26·1 months (IQR 19·1–33·1). No significant difference in early discontinuation of adjuvant endocrine therapy was observed between groups (post-hoc analysis; appendix p 22).

There were 351 invasive disease-free survival events, in 170 of 2883 patients in the palbociclib plus endocrine therapy group and in 181 of 2877 patients in the endocrine therapy alone group; 230 (65·5%) of 351 invasive disease-free survival events were distant recurrences (114 in the palbociclib plus endocrine therapy group *vs* 116 in the endocrine therapy alone group; appendix p 1). At a median follow-up of 23·7 months (IQR 16·9–29·2), invasive disease-free survival did not differ significantly between the two groups, with a 3-year invasive disease-free survival of 88·2% (95% CI 85·2–90·6) in the palbociclib plus endocrine therapy group, and 88·5% (85·8–90·7) in the endocrine therapy alone group (HR 0·93 [95% CI 0·76–1·15]; log-rank p=0·51; figure 2A). Distant recurrence-free survival also did not differ significantly between the two groups (3-year distant recurrence-free survival was 89·3% [95% CI 86·3–91·7; 136 events] in the palbociclib plus endocrine therapy group *vs* 90·7% [88·1–92·8; 135 events] in the endocrine therapy alone group; HR 1·00 [95% CI 0·79–1·27]; log-rank p=0·9997; figure 2B). Primary and secondary efficacy outcomes are described in the appendix (p 2); overall survival data were immature at the time of this analysis. The distribution of censoring times was similar between groups (data not shown). At the second interim analysis, the test statistic comparing invasive disease-free survival between groups crossed the prespecified futility boundary, leading the independent data monitoring committee to recommend the discontinuation of palbociclib in patients receiving palbociclib plus endocrine therapy and moving all patients to the follow-up phase of

	Palbociclib plus endocrine therapy group	Endocrine therapy alone group
Initiated palbociclib	2840	..
Ongoing palbociclib at data cutoff	725 (25·5%)	..
Completed palbociclib per protocol	916 (32·3%)	..
Early discontinuation of palbociclib	1199 (42·2%)*	..
Adverse events (including unacceptable toxicity)	770 (27·1%)	..
Patient non-compliance or non-adherence	128 (4·5%)	..
Development of recurrent disease or secondary malignancy	104 (3·7%)†	..
Informed consent withdrawal	100 (3·5%)	..
Other reasons	97 (3·4%)	..
Initiated endocrine therapy	2840	2903
Ongoing endocrine therapy at data cutoff	2462 (86·7%)	2500 (86·1%)
Ongoing endocrine therapy at end of study participation	182 (6·4%)	219 (7·5%)
Early discontinuation of endocrine therapy	196 (6·9%)	184 (6·3%)
Development of recurrent disease or secondary malignancy	86 (3·0%)†	84 (2·9%)
Informed consent withdrawal	49 (1·7%)	39 (1·3%)
Adverse events (including unacceptable toxicity)	28 (1·0%)	23 (0·8%)
Patient non-compliance or non-adherence	12 (0·4%)	10 (0·3%)
Other reasons	21 (0·7%)	28 (1·0%)

Data are n (%). *At time of data cutoff, 1199 patients had discontinued palbociclib among 2840 patients who had initiated palbociclib. Estimates of palbocilib discontinuation accounting for censoring due to the ongoing nature of the study are summarised in the main text. †At the time of the invasive disease-free survival event, discontinuation of palbocicilb was required per protocol, but not required for adjuvant endocrine therapy.

Table 2: **Treatment status and reasons for early discontinuation of palbociclib and endocrine therapy**

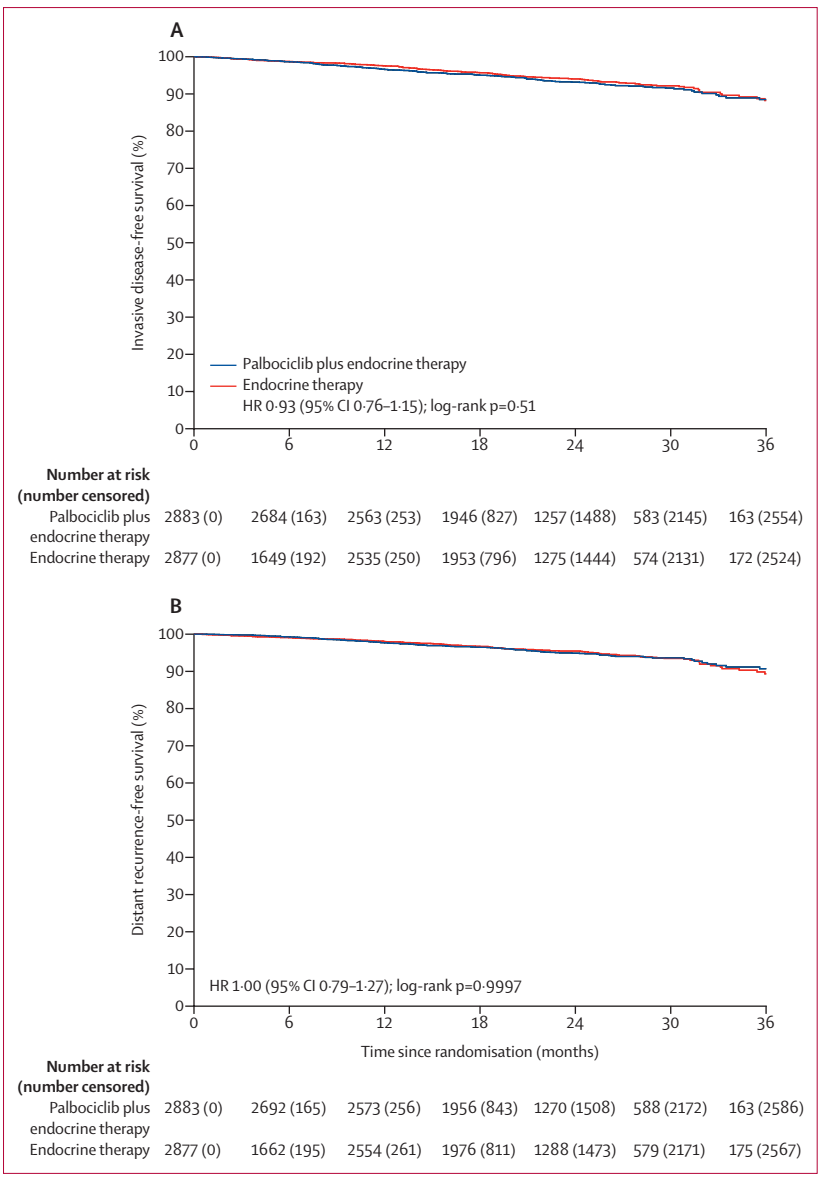

***Figure 2*: Primary and key secondary outcomes in the intention-to-treat population**
(A) Invasive disease-free survival (primary outcome). (B) Distant recurrence-free survival. HR=hazard ratio.

the study—a recommendation approved by the PALLAS steering committee.

Post-hoc analyses were done to evaluate subgroups of patients who might have benefited from adjuvant palbociclib therapy. No clinicopathological subgroup appeared to benefit from the addition of palbociclib to standard adjuvant endocrine therapy. (figure 3).

5743 patients were included in the safety population; 2840 on palbociclib plus endocrine therapy, and 2903 on endocrine therapy alone. Treatment-emergent adverse events occurred in 2822 (99·4%) of 2840 patients on palbociclib and endocrine therapy and in 2571 (88·6%) of 2903 patients on endocrine therapy alone (table 3; appendix pp 3–20). The most common grade 3–4 adverse events were neutropenia (1742 [61·3%] of 2840 patients on palbociclib and endocrine therapy *vs* 11 [0·3%] of 2903 on endocrine therapy alone), leucopenia (857 [30·2%] *vs* three [0·1%]), and fatigue (60 [2·1%] *vs* ten [0·3%]). Febrile neutropenia was uncommon (28 [1·0%] patients on palbociclib and endocrine therapy *vs* none [0·0%] on endocrine therapy alone). Among patients on palbociclib plus endocrine therapy, the rate of grade 3–4 neutropenia was 63·1% (1487 of 2355) in patients with previous chemotherapy exposure, versus 52·6% (255 of 485) in patients without. No new safety signals were identified, the safety profile was consistent with previously reported data, and no treatment-related deaths were observed. Post-hoc analysis of time to first palbociclib dose reduction to 100 mg and 75 mg is shown in the appendix (p 23). The cumulative proportion of patients requiring at least one dose reduction of palbociclib to 100 mg was 42·2% (95% CI 40·3–44·0) by 6 months, 48·9% (47·1–50·8) by 12 months, 53·5% (51·6–55·3) by 18 months, and 55·4% (53·6–57·3) by 24 months. The cumulative proportion of patients requiring at least one dose reduction of palbociclib to 75 mg was 17·3% (95% CI 15·9–18·7) by 6 months, 25·9% (24·3–27·5) by 12 months, 30·5% (28·8–32·2) by 18 months, and 34·3% (32·4–36·1) by 24 months. Post-hoc analysis of specific adverse events showed that interstitial lung disease occurred in 15 (0·5%) of 2840 patients on palbociclib and endocrine therapy versus five (0·2%) of 2903 patients on endocrine therapy alone. Venous thromboembolism and related thrombotic adverse events occurred in 47 (1·7%) versus 20 (0·7%) patients. Serious adverse events occurred in 351 (12·4%) of 2840 patients on palbociclib plus endocrine therapy versus 220 (7·6%) of 2903 patients on endocrine therapy alone. The most common serious adverse events were tissue infection (49 [1·7%] patients on palbociclib and endocrine therapy *vs* 29 [1·0%] on endocrine therapy alone), and upper respiratory tract infection (23 [0·8%] *vs* three [0·1%]).

Discussion

In this second interim analysis of the PALLAS trial, the addition of palbociclib to adjuvant endocrine therapy did not improve invasive disease-free survival compared with endocrine therapy alone in patients with stage II–III hormone-receptor-positive, HER2-negative breast cancer. This analysis was done after 67% of expected invasive disease-free survival events had occurred, and a futility boundary had been crossed. In the treatment group, 42% of patients stopped palbociclib prematurely, primarily because of adverse events. No new adverse events were observed in patients receiving palbociclib compared with the metastatic breast cancer setting. Analyses of clinicopathological subgroups, including a high-clinical-risk cohort, did not identify a subpopulation of patients benefiting from adjuvant palbociclib. In addition to the

	Palbociclib plus endocrine therapy group		Endocrine therapy alone group		Hazard ratio (95% CI)	$P_{interaction}$
	Events n/N	3-year invasive disease-free survival (95% CI)	Events n/N	3-year invasive disease-free survival (95% CI)		
Stage						0·99
IIA	21/504	94·7 (91·4–96·7)	25/509	92·9 (88·9–95·5)	0·91 (0·51–1·63)	
IIB or III	149/2370	85·6 (81·4–89·0)	156/2359	86·6 (82·7–89·6)	0·92 (0·73–1·15)	
T stage						0·60
T0, T1, Tis, or TX	26/557	92·8 (88·9–95·4)	22/500	93·3 (89·3–95·8)	1·10 (0·62–1·94)	
T2	84/1603	90·0 (86·4–92·7)	101/1636	89·0 (85·5–91·7)	0·84 (0·63–1·12)	
T3 or T4	60/722	79·8 (69·8–86·8)	58/741	82·4 (73·6–88·5)	1·01 (0·70–1·44)	
N Stage						0·50
N0	14/367	95·5 (92·3–97·4)	23/383	89·4 (83·0–93·5)	0·65 (0·33–1·26)	
N1	53/1427	93·7 (91·4–95·5)	53/1415	93·4 (90·2–95·6)	1·02 (0·70–1·50)	
N2 or N3	103/1088	75·0 (65·9–82·0)	105/1079	79·3 (71·7–85·1)	0·89 (0·68–1·17)	
Histological grade						0·56
G1 or G2	86/1922	91·0 (87·9–93·3)	100/1971	90·6 (87·5–93·0)	0·88 (0·66–1·18)	
G3	73/836	83·2 (76·2–88·4)	71/767	82·8 (76·7–87·5)	0·89 (0·65–1·24)	
GX	11/122	76·5 (42·5–92·0)	9/139	89·6 (78·6–95·1)	1·43 (0·59–3·44)	
Adjuvant or neoadjuvant chemotherapy						0·36
No	18/498	94·9 (91·4–97·0)	27/507	91·7 (86·7–94·8)	0·71 (0·39–1·28)	
Yes	152/2384	85·9 (81·7–89·1)	154/2370	87·4 (84·0–90·1)	0·96 (0·77–1·20)	
Age group, years						0·29
≤50	79/1309	85·9 (79·8–90·2)	73/1304	88·6 (86·7–94·8)	1·06 (0·77–1·45)	
>50	91/1573	89·7 (86·5–92·2)	154/1370	87·4 (84·0–90·1)	0·84 (0·64–1·11)	
Clinical risk						0·87
High	131/1710	81·9 (76·1–86·4)	136/1672	83·6 (78·7–87·7)	0·89 (0·70–1·13)	
Low	29/1172	95·0 (92·8–96·5)	45/1205	93·1 (89·8–95·3)	0·93 (0·61–1·43)	
All patients	**170/2883**	**88·2 (85·2–90·6)**	**181/2877**	**88·5 (85·8–90·7)**	**0·93 (0·75–1·14)**	

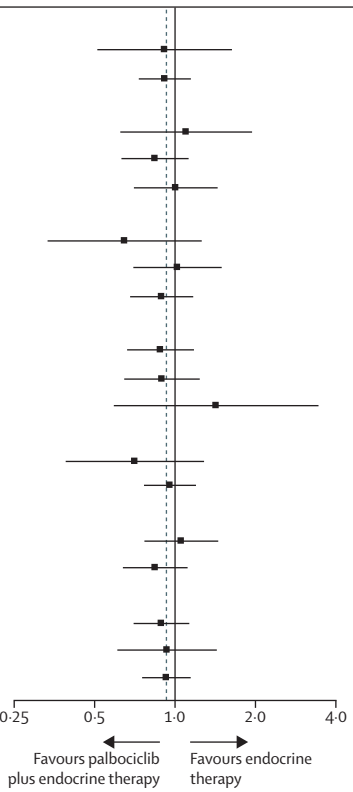

Figure 3: **Subgroup analyses of invasive disease-free survival**
High clinical risk disease includes: more than four nodes involved (>N2), or one to three nodes with either T3 or T4 or grade 3 disease, or both.

continued long-term follow-up that is essential to examine long-term outcomes in patients with hormone-receptor-positive luminal breast cancer, an ongoing translational science programme will explore patient subgroups to identify tumour biology features that might predict benefit from adjuvant palbociclib therapy.

There are several potential explanations for the observed lack of benefit of palbociclib in the PALLAS trial. One consideration is whether the drug duration or exposure, or both, were adequate. A substantial proportion of patients in the palbociclib plus endocrine therapy group stopped palbociclib before 2 years, and lack of adequate exposure to palbociclib might have prevented an accurate evaluation of drug benefit. Much of the early discontinuation was protocol-mandated and related to neutropenia. Early discontinuation persisted despite active outreach efforts to reduce non-protocol-mandated discontinuations. As it is not known which combination of treatment duration and dose intensity best comprises adequate CDK4/6 inhibitor exposure in the early breast cancer setting, additional ongoing exploratory analyses will fully characterise the impact of early discontinuation and variable exposure of palbociclib on efficacy outcomes. Additionally, analysis of patient-reported outcomes and adherence questionnaires will offer insight into the experience of receiving adjuvant palbociclib and impact on adherence to oral therapies.

An additional explanation for the results of the PALLAS trial relates to the tumour type under study. Hormone-receptor-positive breast cancer is a heterogeneous disease, comprising both indolent luminal A-like cancers (which might be more hormone driven and have greater sensitivity to endocrine therapies) and proliferative luminal B-like cancers (which have a higher risk of early recurrence, primary endocrine resistance, and potentially greater sensitivity to chemotherapy-like therapies).[23] It is not well established whether palbociclib provides greater benefit to one biological subgroup versus another, although no indication of preferential benefit by subgroup has been observed in the metastatic setting.[24] However, as early invasive disease events are likely to represent luminal B disease, more time must elapse

	Palbociclib plus endocrine therapy (n=2840)					Endocrine therapy alone (n=2903)				
	Grade 1–2	Grade 3	Grade 4	Grade 5*	Grade unknown	Grade 1–2	Grade 3	Grade 4	Grade 5*	Grade unknown
Any adverse event	752 (26·5%)	1897 (66·8%)	159 (5·6%)	14 (0·5%)	0	2132 (73·4%)	400 (13·8%)	24 (0·8%)	11 (0·4%)	4 (0·1%)
Neutropenia	611 (21·5%)	1620 (57·0%)	122 (4·3%)	0	1 (0·0%)	126 (4·3%)	11 (0·4%)	0	0	2 (0·1%)
Leucopenia	693 (24·4%)	843 (29·7%)	14 (0·5%)	0	0	209 (7·2%)	3 (0·1%)	0	0	1 (0·0%)
Fatigue	1090 (38·4%)	60 (2·1%)	0	0	0	535 (18·4%)	10 (0·3%)	0	0	1 (0·0%)
Arthralgia	961 (33·8%)	30 (1·1%)	0	0	1 (0·0%)	1176 (40·5%)	31 (1·1%)	0	0	0
Upper respiratory tract infection	771 (27·1%)	32 (1·1%)	0	0	2 (0·1%)	450 (15·5%)	3 (0·1%)	0	0	0
Hot flush	683 (24·0%)	7 (0·2%)	0	0	3 (0·1%)	831 (28·6%)	7 (0·2%)	0	0	0
Anaemia	650 (22·9%)	13 (0·5%)	0	0	1 (0·0%)	153 (5·3%)	4 (0·1%)	0	0	0
Thrombocytopenia	583 (20·5%)	25 (0·9%)	1 (0·0%)	0	0	48 (1·7%)	1 (0·0%)	0	0	0
Nausea	535 (18·8%)	8 (0·3%)	0	0	0	236 (8·1%)	4 (0·1%)	0	0	0
Alopecia†	496 (17·5%)	0	0	0	0	143 (4·9%)	0	0	0	1 (0·0%)
Diarrhoea	446 (15·7%)	21 (0·7%)	0	0	1 (0·0%)	140 (4·8%)	5 (0·2%)	0	0	0
Headache	426 (15·0%)	7 (0·2%)	0	0	2 (0·1%)	315 (10·9%)	7 (0·2%)	0	0	0
Cough	388 (13·7%)	1 (0·0%)	0	0	3 (0·1%)	208 (7·2%)	0	0	0	0
Constipation	387 (13·6%)	0	0	0	1 (0·0%)	164 (5·6%)	0	1 (0·0%)	0	1 (0·0%)
Insomnia	360 (12·7%)	7 (0·2%)	0	0	1 (0·0%)	346 (11·9%)	4 (0·1%)	0	0	0
Lymphopenia	264 (9·3%)	95 (3·3%)	5 (0·2%)	0	0	111 (3·8%)	8 (0·3%)	1 (0·0%)	0	0
Rash	321 (11·3%)	6 (0·2%)	0	0	0	140 (4·8%)	3 (0·1%)	0	0	1 (0·0%)
Lymphoedema	312 (11·0%)	3 (0·1%)	0	0	0	250 (8·6%)	2 (0·1%)	0	0	2 (0·1%)
Hypertension	152 (5·4%)	41 (1·4%)	0	0	1 (0·0%)	157 (5·4%)	59 (2·0%)	0	0	0

Data are n (%). Adverse events shown are regardless of attribution; the table summarises all grade 1–2 events occurring in 10% or more patients, all grade 3 events occurring in 1% or more patients, all grade 4 events occurring in 1% or more patients, and all grade 5 events (deaths) occurring in more than 1% of patients. *No deaths were attributed to protocol therapy. †Palbociclib plus endocrine therapy: grade 1, n=460 (16·2%), grade 2, n=36 (1·3%); endocrine therapy: grade 1, n=135 (4·7%), grade 2, n=8 (0·3%).

Table 3: **Maximum grade adverse events in the safety population**

before the benefit of palbociclib across all hormone-receptor-positive breast cancer subtypes can be fully understood.

The discrepancy between the efficacy of palbociclib in the metastatic versus adjuvant setting might also be explained by differences in tumour biology relevant to the mechanism of action of palbociclib. Current models of hormone-receptor-positive, HER2-negative breast cancer recurrence suggest sequestration of a proliferative cell population in the bone marrow and other sites.[25] A non-proliferative dormant phase of varying duration might be followed by subsequent escape from dormancy, characterised by the return of proliferating cells to the circulation.[26] In preclinical models, prolonged exposure to CDK4/6 inhibitors and associated cell-cycle arrest can result in irreversible cellular senescence.[27] Clinically, palbociclib has a strong antiproliferative effect on early-stage disease in the neoadjuvant setting; however, this effect could be reversible with treatment cessation[28] and does not appear to improve clinical response rate over endocrine therapy alone.[29] As palbociclib is dosed intermittently, the on–off schedule might have reversed the antiproliferative effects of palbociclib that are necessary for induction of full senescence within micrometastatic disease. This mechanism might not be applicable to macrometastatic disease, as intermittent versus continuous palbociclib dosing in the metastatic setting shows similar outcomes.[30] Overall, successful strategies for reducing proliferating macrometastatic disease in the metastatic setting might differ from approaches in the adjuvant setting targeting micrometastatic dormant tumour cells.[31] The extensive TRANS-PALLAS biobank of tumour and blood samples will be instrumental in elucidating these and other possible biological explanations for the observed results.

There are limitations to this analysis of the PALLAS trial. This interim report represents only 2 years of initial median follow-up and a lower number of events needed than planned for the final analysis. As the risk of hormone receptor-positive breast cancer recurrence extends over many years, the accumulation of further events in the ongoing long-term follow-up might provide more comprehensive information about the effects of palbociclib exposure. Additionally, the PALLAS trial was intentionally designed with broad eligibility criteria to capture a wide range of tumour stages resembling routine clinical practice. It is possible that a small subset of patients with biologically sensitive disease derived benefit from palbociclib, but with the efficacy signal being non-detectable within the entire trial population.

The PALLAS trial represents an important global collaboration between academia, community practice, and industry, rapidly achieving its desired target accrual

to answer an important question about the management of breast cancer. The results of the PALLAS study remind us that benefits observed in the metastatic setting do not necessarily translate into the adjuvant setting, underscoring the importance of doing well designed adjuvant trials to determine the potential efficacy of such therapies. Ongoing long-term follow-up of patients and additional clinical and translational analyses in the PALLAS trial will continue to explore the effect of palbociclib exposure in these patients, as well as address questions about the contemporary management of hormone-receptor-positive, HER2-negative breast cancer.

Contributors

ELM, ACD, CF, MGn, AD, CHB, MK, HJB, KDM, GP, OMF, EPW, and ACW contributed to the literature search. ACD and CF contributed to the figures. ELM, ACD, CF, MGn, AD, CHB, MK, HJB, KDM, GP, OMF, EPW, ACW, and HF contributed to study design. ELM, ACD, CF, MGn, AD, CD, HF, MS, GP, and OMF contributed to data collection. ELM, ACD, CF, MGn, AD, GP, OMF, CD, HF, and MS contributed to data analysis and interpretation. All authors contributed to the writing of the manuscript. ACD and CF accessed and verified the data.

Declaration of interests

ELM reports personal fees from Eisai, Lilly, and Novartis, outside the submitted work. MM reports grants and personal fees from Roche and Novartis; grants from PUMA; and personal fees from Lilly, Pfizer, AstraZeneca, Taiho Oncology, Amgen, Pharmamar, and Daiichi Sankyo, outside the submitted work. GR reports personal fees from Pfizer, Novartis, and Lilly, outside the submitted work. MB-E reports personal fees from Pfizer, Novartis, and Lilly, outside the submitted work; and travel expenses from Pfizer and Roche. NZ reports grants from ABCSG, during the conduct of the study; personal fees from Roche, Amgen, Eisai, Eli Lilly, and Pfizer, outside the submitted work; and grants from Roche, outside the submitted work. EPW reports personal fees from Carrick Therapeutics, G1 Therapeutics, Genomic Health, GSK, Jounce, Leap, Lilly, Novartis, Seattle Genetics, Syros, and Zymeworks; and grants and personal fees from Genentech/Roche, outside the submitted work. 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DF reports grants from Pfizer, during the conduct of the study; and grants from AstraZeneca, Novartis, Roche/Genentech, Servier, and Tesaro, outside the submitted work. KPT is an employee of Pfizer. DRL is an employee of Pfizer and owns Pfizer stock. CHB was an employee of Pfizer (until 2019) and reports personal fees from Pfizer during the conduct of the study. MK was an employee of Pfizer (until 2017) and is a shareholder of Pfizer, and was employed at Repare Therapeutics, during the conduct of the study. CF reports grants from Pfizer, during the conduct of the study. AD reports grants from the Alliance Foundation for Clinical Trials, during the conduct of the study; personal fees from Pfizer and Context Therapeutics; grants from Novartis, Pfizer, Genentech, Calithera, and Johnson and Johnson, outside the submitted work; and AD's spouse is on a data safety monitoring board for a Pfizer drug not for use in oncology. MGn reports personal fees from Amgen, Daiichi Sankyo, AstraZeneca, Eli Lilly, LifeBrain, Nanostring, Novartis, and TLC Biopharmaceuticals, all outside the submitted work; and an immediate family member is employed by Sandoz. ACD, HJB, KDM, DA, FH, AL, SAN, MS, and CD declare no completing interests.

Data sharing

Pseudonymised individual participant data will be made available after completion of the study (ie, at the end of the follow-up phase) at the latest; the specific data made available will depend on the data needed to answer the question in the application. Other documents that will be available include the master informed consent form, the study protocol and amendments, and the PALLAS Policy for Access to Study Data or Surplus Samples for Research Projects not related to the protocol (policy). We will share data with researchers whose proposed use of the data has been approved according to the PALLAS Policy for Access to Study Data or Surplus Samples for Research Projects not related to the protocol (policy), and whose research purpose is in line and approved according to the policy. Excluded research include a research project for the benefit of any commercial or for-profit entity to develop (A) any product intended for use in the cure, mitigation, treatment, or prevention of disease in man or other animals ("Therapeutic Product"), or (B) any diagnostic product intended for the use in connection with any Therapeutic Product, whose primary method of action is modulation of the target known as CDK 4/6. This restriction does not prevent or preclude development of other diagnostic product development. Proposals should be directed to pallas.proposals@abcsg.at and

pallas_aft@alliancefoundationtrials.org to request access. Data will be made available after approval of a research proposal according to the policy and with a signed data transfer agreement.

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For more on the **Austrian Breast and Colorectal Cancer Study Group** see https://www.abcsg.com

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