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Outcomes in stage IIA versus stage IIB/III in the PALLAS trial [ABCSG-42/AFT-05/PrE0109/BIG-14-13])

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Abstract

Background The PALLAS trial investigated the addition of palbociclib to standard adjuvant endocrine therapy to reduce breast cancer recurrence. This pre-specified analysis was conducted to determine whether adjuvant palbociclib benefited patients diagnosed with lower risk stage IIA disease compared to those with higher stage disease.

Methods PALLAS was an international, multicenter, randomized, open-label, phase III trial, representing a public–private partnership between Pfizer, the Austrian Breast Cancer Study Group, and the U.S. ALLIANCE Foundation. Patients diagnosed with stage II–III, hormone-receptor-positive, HER2/neu negative breast cancer within 12 months of diagnosis had completed all definitive therapy aside from endocrine therapy (started within 6 months prior to study entry) were eligible. All patients were required to submit a formalin-fixed paraffin-embedded (FFPE) tumor block. Patients were randomly assigned 1:1 to receive standard adjuvant endocrine therapy (of physicians' choice) for at least 5 years with or without 2 years of palbociclib, administered orally at a starting dose of 125 mg daily, given for 21 days followed by a 7-day break.

Results A total of 5,796 patients with HR + /HER2- early breast cancer (including 1,010 with stage IIA) were enrolled. Median follow-up was 50 months for stage IIA patients and 43.1 months overall. In the stage IIA cohort, 4-year iDFS in the palbociclib arm was 92.9% versus 92.1% for ET alone (HR 0.75, 95%CI 0.48–1.19, $p = 0.23$). There was no differential benefit by histologic grade, chemotherapy receipt, age, or anatomic/clinical risk. Additionally, no benefit to palbociclib was seen in this cohort in invasive breast cancer-free survival (iBCFS), locoregional relapse-free survival (LRFS), distant relapse-free survival (DRFS), or overall survival (OS). For the stage IIB/III patients, 4-year iDFS was 85.3% for palbociclib + ET versus 83.6% for ET alone (HR 0.91, 95% CI 0.77–1.07, $p = 0.24$).

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Conclusions and relevance While there were substantial differences in outcome for stage IIA versus IIB/III patients at 4 years of follow-up, the addition of 2 years of palbociclib did not improve outcomes for patients, regardless of stage.

Trial Registration ClinicalTrials.gov number NCT02513394 Registered 30 Jul 2015.

Keywords Adjuvant, Endocrine, CDK4/6 inhibitor, Stage II breast cancer

Background

CDK4/6 inhibitors counteract the loss of cell cycle control in hormone receptor-positive, HER2-negative breast cancer. In metastatic disease, the combination of a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) and endocrine therapy (ET) prolongs progression-free and overall survival and is well tolerated [1–3]. Several large adjuvant trials of these agents are ongoing, with both abemaciclib and ribociclib currently FDA-approved for this indication [4, 5]. The PALLAS trial is a global phase III trial investigating whether the addition of the CDK4/6 inhibitor palbociclib to adjuvant ET improves outcomes compared to ET alone in this setting [6, 7]. The first report of PALLAS results occurred after the planned second interim analysis, which determined that two years of adjuvant palbociclib with ET did not improve iDFS compared to adjuvant ET alone [7]; this was confirmed in the protocol-specified, full analysis [6]. Here we report the results of a prespecified, event-driven analysis of the PALLAS stage IIA cohort and an update on the overall intent-to-treat (ITT) study population with additional follow-up.

Methods

Study design

Details of the study design of the PALLAS trial have been published previously [6]. The PALLAS trial is an international, phase III, randomized, open label adjuvant trial. Eligible patients had stage II-III, hormone-receptor-positive, HER2/neu negative disease. They were within 12 months of diagnosis and had completed all definitive therapy aside from ET, and within 6 months of starting adjuvant ET. All patients were required to submit a formalin-fixed paraffin-embedded (FFPE) tumor block to be enrolled. Stratification factors included stage, receipt of chemotherapy, age, and geographic region. Notably, Ki-67 assessment was not mandated and was not collected. Site-specific institutional review boards approved the study protocol and all amendments. All patients provided written informed consent.

Patients were randomized 1:1 to either standard ET with the addition of palbociclib at a starting dose of 125 mg daily, on a 3 weeks on/1 week off schedule, or to standard ET alone. The type of ET was left to the treating clinician and patient and could include any standard of care regimen with a planned duration of treatment of at least 5 years.

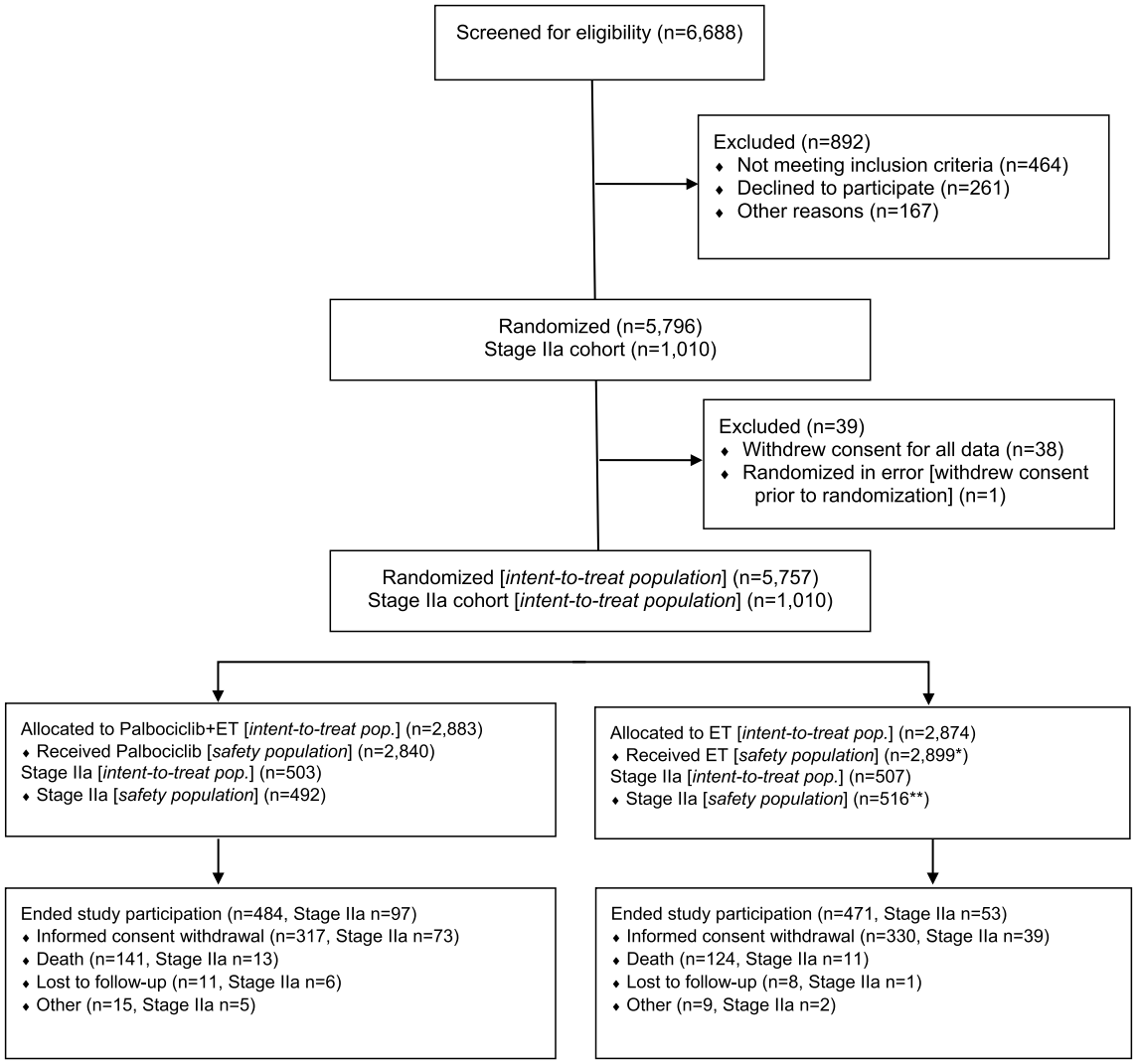
The primary endpoint was invasive disease-free survival (iDFS) by Standardized Definitions for Efficacy End Points (STEEP) criteria requiring a sample size of 5,600 patients to detect a target hazard ratio (HR) of 0.75. Stage IIA enrollment was capped at 1,000 patients to assure that this important subpopulation was included in the trial but not over-represented due to their high prevalence. The final analysis of the PALLAS ITT population was based on 516 events that occurred at 31 months of follow-up. This prespecified secondary analysis of the stage IIA cohort was triggered when an 8% iDFS event rate was reached in the stage IIA ET alone arm, which occurred on December 2, 2021, and included 45 events. The purpose of this analysis was to make a reliable estimate of the treatment effect on iDFS with a sufficient number of events in stage IIA patients. The number of events was not selected based on statistical power considerations. Additional secondary endpoints in this planned analysis included invasive breast cancer-free survival (iBCFS), locoregional relapse-free survival (LRFS), distant relapse-free survival (DRFS) and overall survival (OS) as defined in STEEP.

Comparison of outcomes between randomized arms was based on the ITT principle excluding patients who withdrew consent for use of all data or prior to randomization. Endpoints were summarized using the Kaplan–Meier method, and 4-year rates were estimated with 95% confidence intervals (CIs). Comparisons between arms used log-rank tests stratified by neo/adjuvant chemotherapy (yes vs. no) and age (≤ 50 years vs. >50 years) as recorded at randomization. Hazard ratios (HR) with 95% CIs were estimated using stratified Cox proportional hazards regression models. Comparison of iDFS between arms within subgroups based on patient and clinicopathologic factors used unstratified Cox models. Two-sided p-values <0.05 were considered statistically significant. The approach to data collection and monitoring was previously reported [6]. All data through December 2, 2021, were included in statistical analysis using SAS software (version 9·4).

Results

From September 2015 to November 2018, 5,796 patients were randomly assigned, and 5,757 were included in this analysis and disposition is shown in the CONSORT in Fig. 1**.** The stage IIA cohort (n = 1,010) reached the enrollment cap and was closed to screening in September 2017. The prespecified number of events (45 in the ET alone arm) occurred at a median follow-up of 43.1 months for the full ITT cohort and 50 months for the stage IIA cohort.

Table 1 shows the patient characteristics overall, and within the stage IIA and stage IIB/III cohorts in this updated analysis. Patients who withdrew consent for use of all data or prior to randomization, or those found to be stage I on central review are not included. 503 stage IIA patients were randomized to palbociclib plus ET and 507 were randomized to ET alone. Just over half of the stage IIA patients were postmenopausal and just under a third of the patients had high grade tumors. Stage IIA patients were similar to those with stage IIB/III disease, with the exception of prior chemotherapy. As would be expected, the stage IIA patients received chemotherapy less frequently than the stage IIB/III patients, although those in the stage IIA cohort still received chemotherapy in more



*Includes 35 patients from the Palbociclib+ET arm who received ET only.

**Includes 11 patients from the Palbociclib+ET arm who received ET only.

Fig. 1 shows the CONSORT diagram for this analysis

Table 1 Patient characteristics

Variable	Stage IIA (N = 1,010 patients randomized [intent to treat])		Stage IIB/III (N = 4,728 patients randomized [intent to treat])	
	Palbociclib + Endocrine therapy (N = 503)	Endocrine therapy (N = 507)	Palbociclib + Endocrine therapy (N = 2,371)	Endocrine therapy (N = 2,357)
Age, Years (median, range)	55 (29–84)	53 (30–85)	51 (25–90)	51 (22–85)
Sex (at birth)				
Female	500 (99.4%)	505 (99.6%)	2357 (99.4%)	2341 (99.3%)
Male	3 (0.6%)	2 (0.4%)	14 (0.6%)	16 (0.7%)
Menopausal status				
Postmenopausal	306 (60.8%)	288 (56.8%)	1250 (52.7%)	1241 (52.7%)
Pre/Perimenopausal	194 (38.6%)	216 (42.6%)	1106 (46.6%)	1100 (46.7%)
Unknown/male patient	3 (0.6%)	3 (0.6%)	15 (0.6%)	16 (0.7%)
Histologic grade				
Grade 1/Grade 2	346 (68.8%)	364 (71.8%)	1574 (66.4%)	1596 (67.7%)
Grade 3	145 (28.8%)	127 (25.0%)	690 (29.1%)	640 (27.2%)
Unknown	12 (2.4%)	16 (3.2%)	107 (4.5)	121 (5.1%)
Prior chemotherapy	282 (56.1%)	279 (55.0%)	4,180 (88·4%)	
Clinical risk T/N stage				
T1/N1	254 (50.5%)	250 (49.3%)	–	–
T2/N0	249 (49.5%)	257 (50.7%)	–	–

than 50% of cases and the treatment arms were balanced regarding this factor.

Invasive disease-free survival for stages IIA and IIB/III populations

The iDFS for stage IIA and IIB/III patients is shown in Fig. 2. For patients in the stage IIA cohort (Fig. 2A), 4-year iDFS in the palbociclib + ET arm was 92.9% versus 92.1% for those patients in the ET alone arm, corresponding to a hazard ratio (HR) of 0.75 (95% CI 0.48–1.19, $p = 0.23$). For the stage IIB/III cohort (Fig. 2B), 4-year iDFS was 85.3% for Palbociclib + ET versus 83.6% for ET alone, with corresponding HR of 0.91 (95% CI 0.77–1.07, $p = 0.24$). The p-value for the interaction between arm and stage was not significant (0.46). Thus, regardless of stage group, there was no benefit to adding 2 years of adjuvant palbociclib to standard adjuvant ET. Figure 3 shows the forest plot for iDFS in the stage IIA cohort. No statistically significant benefit between the study arms was seen with regard to histologic grade, receipt of chemotherapy, age, or anatomic clinical risk.

Key secondary endpoints for stage IIA

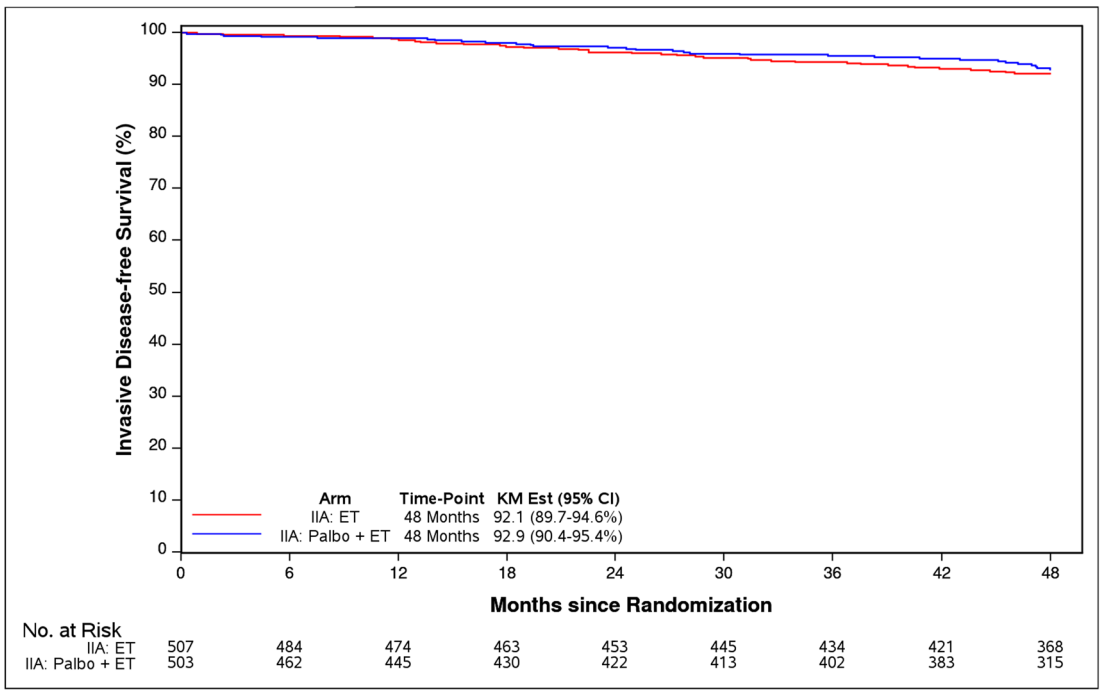
Evaluation of additional key secondary endpoints for the stage IIA patients in the palbociclib + ET versus ET alone groups demonstrated no benefit to palbociclib in 4-year outcomes for iBCFS (94.8% vs. 94.2%, HR 0.80, 95% CI 0.47–1.36), LRFS (98.1% vs. 98.2%, HR 0.84, 95% CI 0.35–2.0), DRFS (95.3% vs. 95.2%, HR 0.92, 95% CI 0.52–1.65) or OS (97.7% vs. 98.1%, HR 1.28, 95% CI 0.57–2.86). The observed 4-year outcomes in the stage IIB/III cohort were as follows: iBCFS (86.6% vs. 85.2%, HR 0.90, 95% CI 0.76–1.06), LRFS (97.1% vs. 96.2%, HR 0.77, 95% CI 0.54–1.10), DRFS (87.5% vs. 86.6%, HR 0.94, 95% CI 0.79–1.12) and OS (93.5% vs. 93.8%, HR 1.13, 95% CI 0.88–1.45).

Discussion

In summary, for patients with stage IIA disease enrolled in the PALLAS trial, the addition of palbociclib to adjuvant ET did not prolong iDFS compared to ET alone. In addition, at 42 months of follow up, there continues to be no benefit detected to the addition of palbociclib in the Stage IIB/III or overall study cohorts. Other planned secondary time-to-event endpoints also did not show a benefit, and notably, there was no benefit observed in those with lower grade disease or in those who did not receive chemotherapy. While no statistically significant benefits to palbociclib were seen, the numbers of patients in each subset were small in this preplanned cohort.

These results from the PALLAS trial continue to contrast with the positive results of the MONARCH-E [4] and NATALEE [8] adjuvant trials. In the MONARCH-E trial, at a median follow up of 42 months, the addition of abemaciclib to adjuvant endocrine therapy continued to show an improvement in IDFS (85.8% abemaciclib + ET vs. 79.4% for ET alone, HR 0.664; 95% CI 0.578–0.762)

a. Stage IIA iDFS



b. Stage IIB/III iDFS

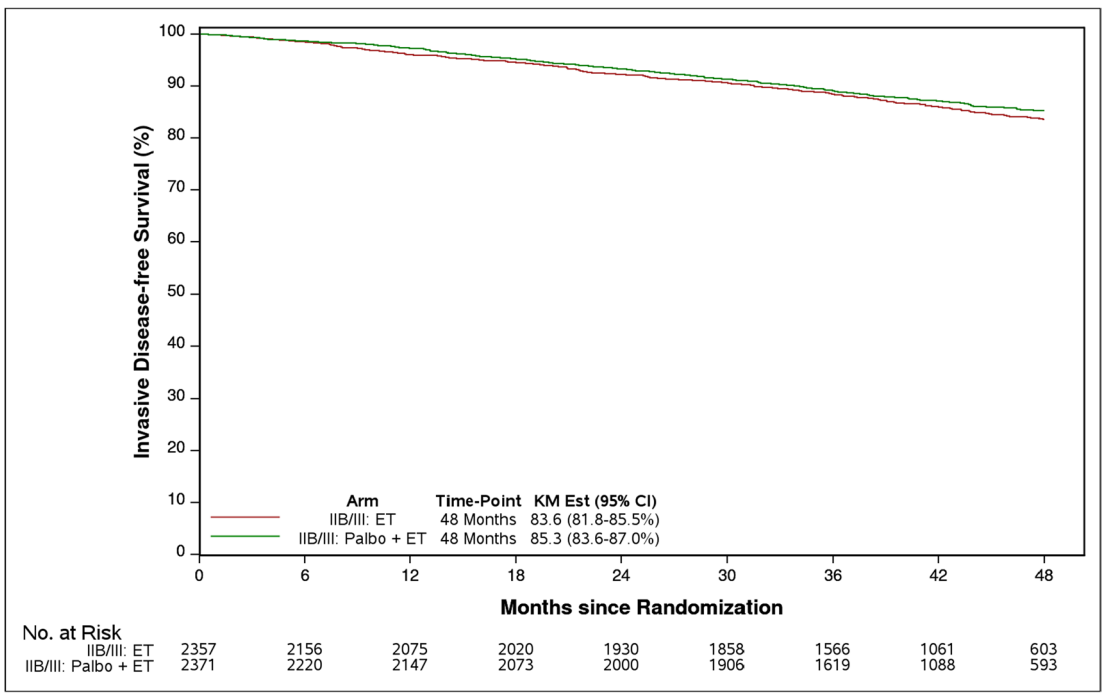


Fig. 2 Shows the Kaplan–Meier plots for invasive Disease-Free Survival (iDFS), the primary endpoint, dichotomized into stage IIA (Fig. 2**a**) and stage IIB/III groups (Fig. 2**b**). There were no significant differences seen between treatment arms in either stage group

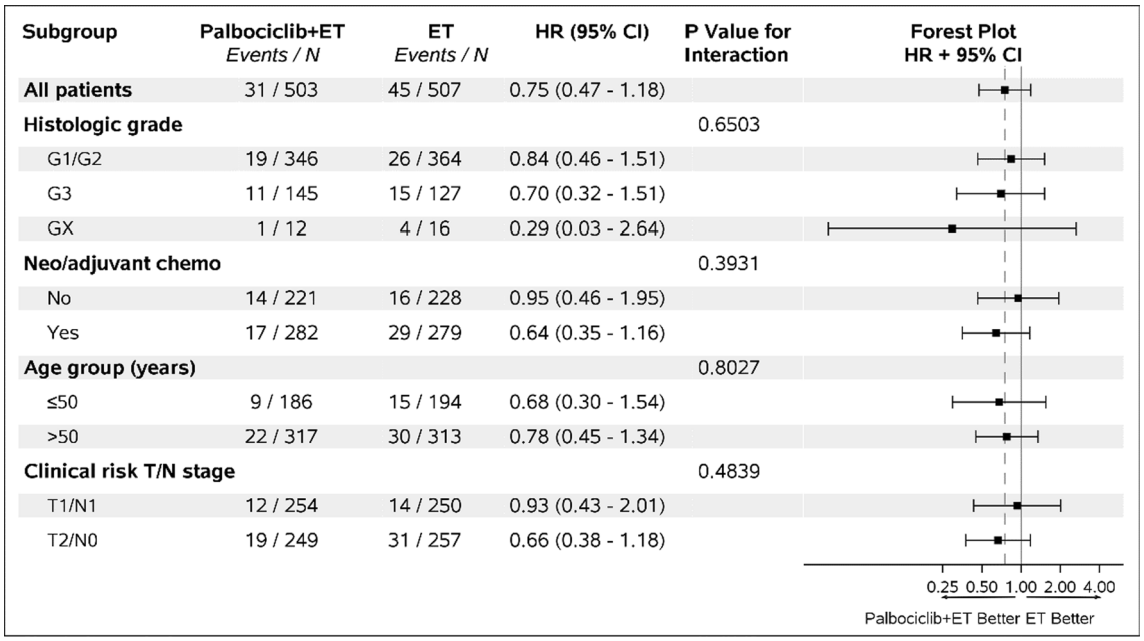


Fig. 3 Shows the Forest Plot indicating the iDFS hazard ratio for Palbociclib plus endocrine therapy versus endocrine therapy alone within prespecified subgroups in the PALLAS trial

[4]. In the NATALEE Trial, at a median follow up of 44.2 months, the addition of ribociclib to adjuvant endocrine therapy also demonstrated a sustained IDFS benefit (88.5% for ribociclib + ET vs. 83.6% for ET alone, HR0.715; 95% CI 0.609–0.840) [9] supporting the recent FDA approval of ribociclib in the adjuvant setting [5]. In both studies, the iDFS benefits also remain statistically significant within stage II and III subgroups. The reasons underlying the differences in outcomes is not clear, though could be related to important differences in CDK target potency between agents or differences in the underlying risk profiles of the study patient populations that extend beyond anatomic stage alone. While adherence has been cited as a possible issue, all three trials had substantial discontinuation rates, and a sensitivity analysis of the PALLAS results based on adherence did not support this hypothesis [10]. It is notable that PALLAS included lower risk, node negative, stage IIA patients without additional high-risk features, distinct from the other trials, and importantly, eligibility for PALLAS was based solely on pathologic stage, using the AJCC version 7 without requiring additional high-risk features such as high Ki-67 or a high-risk genomic test. In this AJCC version, stage IIA includes both patients with N1 (1–3 positive axillary lymph nodes) and patients with T2N0 disease. While MONARCH-E did not enroll any patients with N0 disease, NATALEE did enroll N0 patients, but they were required to have either tumor size > 5 cm, or tumor size 2–5 cm with either Grade 2 (and high genomic risk or Ki67 ≥ 20%) or Grade 3. It is possible that CDK4/6 inhibitors as a class require high proliferative activity to prevent early relapse. But it is notable that at 4 year follow up, the N0 patient population in the NATALEE trial, despite additional high-risk features, did not show a statistically significant benefit from the addition of ribociclib to standard ET (iDFS HR 0.666, 95% CI 0.397–1.118). While this group was included in the current FDA approval of ribociclib, it will be important to determine if a statistically significant iDFS benefit emerges with longer follow up and more events, to ultimately determine the extent of benefit to a lower risk group, albeit not quite as low risk as that in the PALLAS trial. Moreover, additional follow up in both the MONARCH-E and NATALEE trials is necessary to determine whether benefits of abemaciclib and ribociclib in the adjuvant setting extend to reducing late recurrence or improving overall survival. It is worth noting that overall survival benefits with CDK4/6 inhibitors have been difficult to demonstrate in the first-line metastatic setting, with only ribociclib conferring overall survival benefit [5] despite progression-free survival (PFS) benefits for all three cell cycle inhibitors.

Despite a lack of benefit from palbociclib, the PALLAS trial provides an important benchmark for outcomes in ER + breast cancer in an international study population with modern therapy, showing excellent outcomes in both treatment arms among those patients with stage IIA disease. Notably, the risk of recurrence within the ET

control arms differed between PALLAS, MONARCH-E [4], NATALEE [9] and PENELOPE [11] at the same follow-up time. These differences likely reflect important differences in inclusion criteria for stage and other risk factors between the trials that may have further impacted trial results.

Excellent outcomes for patients receiving standard adjuvant therapy begs the question of whether the era of large adjuvant trials based on the clinical stage alone is now past. The results of PALLAS and other large adjuvant trials in ER+ early breast cancer show that while there may be incremental improvements in outcomes, there is also a substantial fraction of patients being exposed to additional therapy who may never relapse. This situation calls for new trial designs and biomarkers that can enrich enrollment for only those patients who will truly benefit from more therapy.

Such an approach requires the ability to identify those patients who are still at risk to enable escalation strategies for those who truly need it. Diagnostic tumor blocks along with serial blood samples were collected on all 5,796 PALLAS participants. This robust biospecimen bank, combined with clinical follow-up and serial bio sample collection over ten years, has enormous potential for additional knowledge generation. Additional investigations include planned correlative analyses of RNA-based gene expression profiles, germline DNA and circulating biomarkers (including ctDNA). Such analyses will enable further investigation of the PALLAS population to evaluate whether there are subpopulations of patients who might benefit from palbociclib and to further our understanding of the biology and natural history of ER+ early breast cancer. Ongoing analyses by the TRANS-PALLAS investigators seek to identify tumors with poor prognosis (using genomic predictors), tumors that respond better to ET (through the SET index and pharmacogenetic markers), and assessment of longitudinal serial blood samples to understand the link between detection of ctDNA and recurrent disease. These studies will help unravel the complex mechanisms of tumor dormancy and reactivation in ER+ disease and have the potential to identify critical biomarkers of poor prognosis and/or imminent relapse that can be utilized in future biomarker enrichment trial designs. Such approaches hold promise in enabling the identification of meaningful therapeutic targets and optimal strategies for surveillance and interception to prevent recurrence in ER+ early breast cancer.

In conclusion, this pre-specified analysis of the PALLAS trial focusing on patients with lower risk stage IIA disease compared to those with higher stage disease failed to demonstrate a benefit to 2 years of adjuvant palbociclib, regardless of stage. Notably, there were substantial differences in outcome for stage IIA versus IIB/III patients at 4 years of follow-up, demonstrating the excellent outcomes for patients with early-stage disease who receive modern adjuvant endocrine therapy, providing a critical benchmark for future studies. Building on these data, the TRANS-PALLAS tumor and serial blood samples will provide further insights of ER+ breast cancer biology.

Abbreviations

ET	Endocrine therapy
IDFS	Invasive disease-free survival
IBCFS	Invasive breast cancer-free survival
LRFS	Locoregional relapse-free survival
DRFS	Distant relapse-free survival
OS	Overall survival
ITT	Intent to treat
FFPE	Formalin-fixed paraffin-embedded
STEEP	Standardized definitions for efficacy end points
HR	Hazard ratio
CIs	Confidence intervals
PFS	Progression-free survival

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Author contributions

A.D. (DeMichele): Contributed to the conception, design of work, acquisition/analyses, drafted and revision, and approved the submitted version. A.D. (Dueck): Contributed to the design of work, acquisition/analyses, drafted and revision, and approved the submitted version. D.H.: Contributed to the design of work, acquisition/analyses, drafted and revision, and approved the submitted version. M.M.: Contributed to the conception and drafted and revision and approved the submitted version. H.B.: Contributed to the conception and drafted and revision and approved the submitted version. G.P.: Contributed to the conception and drafted and revision and approved the submitted version. N.Z.: Contributed to the conception and drafted and revision and approved the submitted version. A.W.: Contributed to the conception and drafted and revision and approved the submitted version. M.B.E.: Contributed to the conception and drafted and revision and approved the submitted version. E.W.: Contributed to the conception and drafted and revision and approved the submitted version. M.B.: Contributed to the conception and drafted and revision and approved the submitted version. K.M.: Contributed to the conception and drafted and revision and approved the submitted version. M.C.: Contributed to the conception and drafted and revision and approved the submitted version. D.L.: Contributed to the conception and drafted and revision and approved the submitted version. G.R.: Contributed to the conception and drafted and revision and approved the submitted version. D.C.: Contributed to the conception and drafted and revision and approved the submitted version. J.B.: Contributed to the conception and drafted and revision and approved the submitted version. C.S.: Contributed to the conception and drafted and revision and approved the submitted version. Z.N.: Contributed to the conception and drafted and revision and approved the submitted version. H.I.: Contributed to the conception and drafted and revision and approved the submitted version. N.W.: Contributed to the conception and drafted and revision and approved the submitted version. K.A.P.: Contributed

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
In the U.S., the study protocol was approved by the institutional review board and the Advarra Protocol Approval number is Pro00034499. Outside the U.S., the trial was approved by respectively responsible institutional review boards and ethics committees. All analyzed patients provided written informed consent, and the trial was performed in strict accordance with ICH GCP guidelines (ClinicalTrials.gov identifier: NCT02513394, EudraCT 2014-005181-30).

Competing interests
Institutional research grants from Novartis, Pfizer, Genentech, and Neogenomics. The authors declare no competing interests.

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