Breast Cancer Research and Treatment (2025) 211:385–397
https://doi.org/10.1007/s10549-025-07653-2

RESEARCH

Impact of adding palbociclib on treatment adherence to ongoing adjuvant endocrine treatment in the global randomized PALLAS randomized trial in patients with early breast cancer

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Received: 5 March 2024 / Accepted: 11 February 2025 / Published online: 27 March 2025

Abstract

Purpose Using patient-reported outcomes (PROs) and more objective measures, we evaluated adherence to adjuvant palbociclib and ET in the PALLAS trial, and the impact of palbociclib on ET adherence.

Methods The open-label, global, phase 3 PALLAS trial randomized patients with hormone receptor-positive (HR+), HER2-negative stage II–III breast cancer (1:1) to either 26 cycles of palbociclib (125 mg/day for 21 days and then 7 days off) plus adjuvant ET, versus ET alone. After 23.7 months median follow-up, palbociclib was stopped due to futility of the intervention and patients were moved to follow-up. For each cycle, daily adherence to ET was measured with study diaries; for palbociclib, study diaries and pill counts. At cycles 2, 3, 6, 12, 18 and 24, patients completed the Morisky Medication Adherence Scale-4 plus an additional item and the McHorney Adherence Questionnaire. Mean persistence was defined in months from treatment initiation to cessation.

Results Four thousand six hundred eighty-eight of 5796 total PALLAS participants were included. Across all cycles, mean daily ET adherence values measured by study diary were > 98.0% and did not differ between treatment arms. Mean persistence to ET was similar between arms (19.2 months for palbociclib + ET vs. 19.6 months for ET alone). However, patient-reported maximal ET adherence was higher across time for palbociclib + ET compared to ET alone ($p \leq 0.0001$, modified MMAS-4; $p = 0.05$, McHorney).

Conclusion In the PALLAS trial, addition of palbociclib did not decrease adherence to adjuvant ET. Though numbers declined over time, daily adherence for palbociclib and ET remained relatively high at each cycle.

Trial Registration: The trial is registered with ClinicalTrials.gov (NCT02513394; 07-31-2015) and EudraCT (2014-005181-30).

Keywords Patient-reported outcomes · Adherence · PALLAS · Adjuvant endocrine therapy · Palbociclib

Introduction

Key discoveries in cancer biology, correlative biomarkers and clinical trials have led to approvals of many new oral anti-cancer therapies, with more treatments in development. As oral anti-cancer therapies are combined with ongoing standard medication regimens, it is unknown how

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the introduction of new agents, each with its own toxicity profile and pill burden, will affect patient adherence with other medications. A recent retrospective analysis of claims data for 2450 cancer patients with comorbid hypertension and hyperlipidemia found that adherence to antihypertensive and statin medications significantly declined after initiating an oral anti-cancer therapy [1]. This was among the first studies reporting the negative impact of combining novel oral cancer therapies with ongoing medication.

Many emerging oral anticancer agents rely on long-term chronic self-administration to be effective. [1, 2] Nonadherence to oral cancer therapies is associated with decreased treatment efficacy [3], decreased survival [4], and increased healthcare utilization. [2] Real world population-based studies estimate that between 30 and 50% of early-stage hormone receptor-positive/HER2-negative (HR+/HER2−) breast cancer patients discontinue endocrine treatment (ET) before reaching 5 years [5, 6]. Unfortunately, this problem has proven relatively intractable to low-cost/ low-touch interventions thus far [7–9].

Palbociclib is an oral cyclin-dependent kinase (CDK) 4/6 inhibitor approved for the treatment of advanced hormone receptor-positive/HER2-negative (HR+/HER2−) breast cancer in combination with ET in first-line and pretreated settings [10–13]. The phase 3 global randomized PALLAS trial (AFT-05, NCT02513394) investigated whether adding 2 years of palbociclib to adjuvant ET improved invasive disease-free survival (iDFS) over adjuvant endocrine therapy alone in stage II-III early invasive HR+/HER2− breast cancer. Interim analysis for the primary endpoint of iDFS did not show a benefit to the 2 year course of palbociclib + ET versus ET-alone [14], however future analyses are planned. Despite a palbociclib early discontinuation rate of over 40% in the trial, post-hoc analyses showed that neither duration of palbociclib treatment nor exposure intensity (number of actual intake days divided by the number of expected intake days for the planned 26 cycles) ≥ the observed median of 70% was significantly related to iDFS at landmark time points of 6, 12, 18, and 24 months [15]. The lack of benefit could not be attributed to ET discontinuation, as those rates were similar between arms (6.9% for palbociclib + ET vs. 6.3% for ET alone) [15].

However, discontinuation is a relatively crude measure of adherence to drug therapy and multimodal measurement methods are recommended to gain a more accurate and detailed sense of treatment adherence [16]. While general rates of adherence to adjuvant CDK4/6 inhibitors + ET vs. ET alone have been published [17], a more comprehensive understanding of patient-level adherence to the CDK 4/6 inhibitor palbociclib and to standard adjuvant ET is desired for patients with early-stage HR+/HER2− breast cancer. Additionally, a deeper exploration of patient adherence to combination therapy versus monotherapy, and any modulation on the ability to maintain adherence to ET, is necessary. Thus, the primary aim of this analysis was to evaluate adherence to palbociclib in combination with adjuvant ET during the PALLAS trial two-year treatment period using study diaries, pill counts and patient-reported measures. A secondary objective was to explore the relationship between iDFS and daily adherence to study drug within each study cycle.

Methods

Design and eligibility

Details of the parent PALLAS trial are described elsewhere [14]. Each participant signed an IRB-approved, protocol-specific informed consent document in accordance with federal and institutional guidelines [14, 15].

Assessing palbociclib, ET adherence

The investigational product palbociclib was distributed to patients by trial staff, whereas adjuvant ET (tamoxifen or aromatase inhibitor with or without luteinizing hormone-releasing hormone [LHRH] agonist) was selected by the treatment provider, could have been initiated before study entry, and was obtained commercially. During each study cycle, all PALLAS trial participants completed study adherence diaries for ET, and those in the palbociclib + ET arm completed separate adherence diaries for palbociclib. Participants randomized to the palbociclib + ET group also underwent palbociclib pill counts; ET pill counts were not performed as it was supplied outside of the trial. Drug diary and pill count data were then used to calculate daily adherence and persistence. Regarding patient-reported adherence outcomes (PROs), a subset intention-to-collect (ITC) population was determined by availability of validated language versions for the PROs of interest. Validated translations of the Morisky medication adherence scale-4item (MMAS-4) were available in English, Spanish, and German; therefore, the ITC population included English-speaking participants in Australia, Ireland, the United Kingdom and the United States (US), Spanish-speaking participants in Mexico and Spain, and German-speaking participants in Austria and Germany. Having been validated only in the US, the McHorney Brief Adherence Estimator was administered to a subset of English-speaking patients in the US.

Timing of adherence measurements

The schedule of assessments was divided into 28 cycles of 28 days each. At each study visit, all participants were asked to return their completed study diaries for ET adherence,

and if randomized to receive palbociclib, a separate study diary for palbociclib. At each visit, diaries were reviewed for accuracy with the patient. Participants randomized to receive palbociclib were also asked to return previously dispensed palbociclib bottles, including unused drug and/or empty bottles, so that study staff could record pill counts. Patients in the ITC PRO population were asked to complete modified MMAS-4 and McHorney adherence paper questionnaires at study visits for cycles 2, 3, 6, 12, 18 and 24.

Scoring of adherence measurements

When measured via study diary, daily adherence was calculated as a percentage for each 28 day cycle (i.e., the number of days that the pills were taken divided by the number of days that the medication should have been taken, thus accounting for treatment interruptions when directed by the provider team). For daily adherence via pill count (palbociclib only), the number of pills taken was always divided by 21, because the number of days due to treatment interruptions as directed by the provider team was not known; thus, prescribed treatment interruptions were counted as nonadherence. Within each randomized arm, adherence was calculated separately for ET using study diary data and, for palbociclib, using study diary and pill count data with any discrepancies resolved with pill count. When measuring treatment adherence to either palbociclib or ET for a particular cycle, only those patients who had initiated that cycle were included. We report mean daily adherence to palbociclib and/or ET, calculated as the average proportion of prescribed pills taken, across all patients who had initiated that cycle. Additionally, the number (N) that initiated each cycle was plotted over time and by arm. Mean and median persistence to treatment within each group was defined as the act of continuing therapy for the prescribed duration; withdrawal from treatment due to protocol-mandated toxicity and iDFS events were not counted. Patients who did not complete the 2 year treatment phase of the protocol for non-iDFS event reasons were moved to long-term follow-up and were allowed to continue their ongoing ET.

Patient-reported adherence to palbociclib and to ET was measured with the 4 item Morisky Medication Adherence scale (MMAS-4) and the 3-item, 6-point Likert response McHorney Brief Estimator. The former assessed intentional and unintentional medication-taking behaviors using a dichotomous yes/no response format and included an additional dichotomized item, "*All things considered, did you actually take your* (Palbociclib/ Anti-hormone pill) *exactly as directed by your doctor?"* Scores from the five items were summed to create a total Morisky composite score, ranging from 0 to 5, with a maximal score of 5 considered "most adherent." The McHorney questionnaire measured three proximal beliefs related to intentional medication nonadherence: perceived need for the medication, perceived cost–benefit, and perceived affordability [18]. Scores range from 0 to 36, with zero indicating lowest risk for intentional nonadherence.

Statistical analysis

Generalized estimating equations tested for the average difference of maximal adherence scores on the modified short-form Morisky (score = 5 vs. score < 5) and McHorney (score = 0 vs. score > 0) across the six time points, adjusted for baseline age, geographic region, first adjuvant ET, race, ethnicity, and clinical factors (TN stage, histology, progesterone receptor, chemotherapy status and baseline Eastern Cooperative Oncology Group (ECOG) score). An interaction analysis was also conducted to test whether the pattern of change in maximally adherent scores differed by arm.

Exploratory conditional landmark and Cox hazards analyses evaluated the relationship between daily adherence to palbociclib and iDFS at 6 and 12 month landmark time points, triggered after awareness of the pre-specified 469 iDFS cases for final analysis in November 2020. Separate analyses were conducted for pill count and drug diary data. Adherence groupings were classified into either < 90% adherence versus ≥ 90% based on adherence up to and including that landmark time. Each landmark population included patients who were alive, free of an iDFS event, in follow-up, and had not discontinued palbociclib for either non-protocol- or protocol-related reasons**.** Adherence groupings were based on non-missing pill counts/drug diaries up to and including each landmark time. Sensitivity analyses were conducted treating missing pill counts/drug diaries at a cycle as 0% adherence (worst-case) when calculating the adherence groupings. Data quality was ensured, and statistical analyses were conducted by the Alliance Statistics and Data Center.

Results

Eighty-one percent ($N = 4688$) of the 5796 PALLAS participants were included in the ITC subpopulation for PROs, including adherence, and were clinically representative of the remaining 1073 patients participating in the trial (Table 1). Overall, 92% of the 4688 patients completed study diaries, pill counts and self-reported adherence scales at baseline and again on at least one subsequent occasion. The median age of the ITC sample was 52 years (IQR ranged from 45.0 to 61.0), 88.5% were white, 5.4% reported being of Hispanic ethnicity and 82.9% had prior chemotherapy exposure.

For patients randomized to the palbociclib + ET arm, the mean proportion of patients who adhered to their daily

Table 1 Participant baseline characteristics, by adherence intention-to-collect population

	Intention-to-collect population ($N=4688$)	Not in intention-to-collect population ($N=1073$)	Total ($N=5761$)
Age (years)			
Median	52.0	52.0	52.0
Range	(22.0–90.0)	(24.0–82.0)	(22.0–90.0)
IQR	(45.0, 61.0)	(45.0, 62.0)	(45.0, 61.0)
Age Group			
< = 50 years	2122 (45.3%)	492 (45.9%)	2614 (45.4%)
> 50 years	2566 (54.7%)	580 (54.1%)	3146 (54.6%)
Unknown	0	1 (0.1%)	1 (0.0%)
Menopausal status			
Postmenopausal	2525 (53.9%)	571 (53.2%)	3096 (53.7%)
Premenopausal (including perimenopausal)	2132 (45.5%)	494 (46.0%)	2626 (45.6%)
Not applicable (male patient)	29 (0.6%)	7 (0.7%)	36 (0.6%)
Unknown	2 (0.0%)	1 (0.1%)	3 (0.1%)
ECOG status at randomized combined			
0	3872 (82.6%)	935 (87.1%)	4807 (83.4%)
1/unknown	816 (17.4%)	138 (12.9%)	954 (16.6%)
Race			
Asian	151 (3.2%)	128 (11.9%)	279 (4.8%)
Black or African American/African Heritage	144 (3.1%)	5 (0.5%)	149 (2.6%)
White	4150 (88.5%)	869 (81.0%)	5019 (87.1%)
Native Hawaiian or other Pacific Islander	11 (0.2%)	1 (0.1%)	12 (0.2%)
American Indian or Alaska Native	34 (0.7%)	2 (0.2%)	36 (0.6%)
Other	72 (1.5%)	1 (0.1%)	73 (1.3%)
Unknown	126 (2.7%)	67 (6.2%)	193 (3.4%)
Ethnicity			
Hispanic or Latino	253 (5.4%)	12 (1.1%)	265 (4.6%)
Not Hispanic or Latino	4129 (88.1%)	907 (84.5%)	5036 (87.4%)
Unknown	306 (6.5%)	154 (14.4%)	460 (8.0%)
Gender (at birth)			
Female	4659 (99.4%)	1066 (99.3%)	5725 (99.4%)
Male	29 (0.6%)	7 (0.7%)	36 (0.6%)
Geographic region			
Europe	1842 (39.3%)	749 (69.8%)	2591 (45.0%)
North America	2382 (50.8%)	173 (16.1%)	2555 (44.3%)
Other	464 (9.9%)	151 (14.1%)	615 (10.7%)
Anatomic Stage			
I	16 (0.3%)	2 (0.2%)	18 (0.3%)
IIA	871 (18.6%)	143 (13.3%)	1014 (17.6%)
IIB	1523 (32.5%)	392 (36.5%)	1915 (33.2%)
III	2278 (48.6%)	535 (49.9%)	2813 (48.8%)
Unknown	0	1 (0.1%)	1 (0.0%)
T-Stage			
T0/T1/Tis/TX	901 (19.2%)	158 (14.7%)	1059 (18.4%)
T2	2593 (55.3%)	646 (60.2%)	3239 (56.2%)
T3/T4	1194 (25.5%)	268 (25.0%)	1462 (25.4%)
Unknown	0	1 (0.1%)	1 (0.0%)
N-Stage			
N0	623 (13.3%)	127 (11.8%)	750 (13.0%)
N1	2313 (49.3%)	529 (49.3%)	2842 (49.3%)

Table 1 (continued)

	Intention-to-collect population ($N=4688$)	Not in intention-to-collect population ($N=1073$)	Total ($N=5761$)
N2	1148 (24.5%)	261 (24.3%)	1409 (24.5%)
N3	603 (12.9%)	155 (14.4%)	758 (13.2%)
NX	1 (0.0%)	0	1 (0.0%)
Unknown	0	1 (0.1%)	1 (0.0%)
Histologic grade			
G1	508 (10.8%)	107 (10.0%)	615 (10.7%)
G2	2650 (56.5%)	632 (58.9%)	3282 (57.0%)
G3	1342 (28.6%)	263 (24.5%)	1605 (27.9%)
GX	185 (3.9%)	70 (6.5%)	255 (4.4%)
Unknown	3 (0.1%)	1 (0.1%)	4 (0.1%)
Estrogen receptor			
Positive	4670 (99.6%)	1070 (99.7%)	5740 (99.6%)
Negative	16 (0.3%)	2 (0.2%)	18 (0.3%)
Unknown	2 (0.0%)	1 (0.1%)	3 (0.1%)
Progesterone receptor			
Positive	4123 (87.9%)	955 (89.0%)	5078 (88.1%)
Negative	497 (10.6%)	117 (10.9%)	614 (10.7%)
Unknown	68 (1.5%)	1 (0.1%)	69 (1.2%)
Neoadjuvant endocrine therapy			
Yes	93 (2.0%)	19 (1.8%)	112 (1.9%)
No	4595 (98.0%)	1053 (98.1%)	5648 (98.0%)
Unknown	0	1 (0.1%)	1 (0.0%)
Type of neoadjuvant endocrine therapy			
Aromatase inhibitor	81 (1.7%)	12 (1.1%)	93 (1.6%)
Tamoxifen	9 (0.2%)	8 (0.7%)	17 (0.3%)
Other	3 (0.1%)	0	3 (0.1%)
First class of non-IP during adjuvant phase			
Aromatase inhibitor	3173 (67.7%)	699 (65.1%)	3872 (67.2%)
Tamoxifen	1499 (32.0%)	373 (34.8%)	1872 (32.5%)
Unknown	16 (0.3%)	1 (0.1%)	17 (0.3%)
Luteinizing hormone-releasing hormone intake during adjuvant phase			
No	3749 (80.0%)	769 (71.7%)	4518 (78.4%)
Yes	939 (20.0%)	304 (28.3%)	1243 (21.6%)
Type of surgery			
Breast conservation	1787 (38.1%)	392 (36.5%)	2179 (37.8%)
Mastectomy	2890 (61.6%)	679 (63.3%)	3569 (62.0%)
Mastectomy + contralateral conservation	11 (0.2%)	1 (0.1%)	12 (0.2%)
Unknown	0	1 (0.1%)	1 (0.0%)
Prior chemotherapy			
Yes	3888 (82.9%)	866 (80.7%)	4754 (82.5%)
No	800 (17.1%)	206 (19.2%)	1006 (17.5%)
Unknown	0	1 (0.1%)	1 (0.0%)
Neoadjuvant chemotherapy	1613 (34.4%)	326 (30.4%)	1939 (33.7%)
Adjuvant chemotherapy	2328 (49.7%)	547 (51.0%)	2875 (49.9%)
Type of chemotherapy			
Anthracycline-based	3387 (72.2%)	800 (74.6%)	4187 (72.7%)
Non-anthracycline	729 (15.6%)	225 (21.0%)	954 (16.6%)
Other	27 (0.6%)	4 (0.4%)	31 (0.5%)

Table 1 (continued)

	Intention-to-collect population ($N=4688$)	Not in intention-to-collect population ($N=1073$)	Total ($N=5761$)
Radiation prior to the 2-year active treatment phase of the PALLAS trial			
Yes	4170 (89.0%)	958 (89.3%)	5128 (89.0%)
No	518 (11.0%)	113 (10.5%)	631 (11.0%)
Unknown	0	2 (0.2%)	2 (0.0%)

palbociclib, as measured by study diaries, was high throughout all cycles, ranging from 93.4% at cycle 1 to 97.9% at cycle 26, peaking at cycle 12 (Table 2). When measured by pill count, the mean adherence for each 28 day cycle was lower, 89.8% at cycle 1, but remained high throughout all cycles (96.5% at cycle 26; data not shown). However,

Table 2 Adherence and persistence to palbociclib and endocrine therapy (ET) via drug diary, by treatment arm

Cycle	Palbociclib + ET arm				ET alone arm	
	Palbociclib		ET		ET	
	Mean adherence (SD[a])	Diary data N^b (percent)	Mean adherence (SD)	Diary data N^b (percent)	Mean adherence (SD)	Diary data N^b (percent)
1	93.4 (13.8)	2153 (94.0%)	98.7 (6.1)	2006 (86.9%)	99.0 (5.2)	1975 (84.3%)
2	94.7 (13.3)	2054 (94.2%)	98.8 (6.4)	1966 (89.2%)	98.4 (7.1)	1966 (89.1%)
3	97.4 (10.1)	1953 (92.5%)	98.7 (7.3)	1906 (89.0%)	98.8 (6.3)	1909 (88.1%)
4	97.6 (10.2)	1898 (93.3%)	98.6 (7.8)	1871 (88.7%)	99.0 (5.7)	1904 (88.4%)
5	97.6 (11.1)	1838 (93.1%)	98.3 (7.9)	1842 (88.0%)	98.1 (8.3)	1897 (88.3%)
6	98.1 (8.7)	1759 (92.6%)	98.7 (6.6)	1826 (89.6%)	98.5 (8.2)	1841 (87.0%)
7	98.1 (9.3)	1731 (93.3%)	99.0 (6.3)	1813 (90.1%)	98.6 (7.3)	1844 (87.7%)
8	98.0 (9.1)	1686 (93.1%)	98.2 (8.2)	1791 (89.7%)	98.1 (8.2)	1821 (87.0%)
9	98.4 (7.4)	1605 (92.6%)	99.0 (6.4)	1767 (90.1%)	98.8 (6.8)	1787 (87.1%)
10	98.3 (8.6)	1583 (92.4%)	99.2 (4.9)	1755 (90.2%)	99.0 (5.5)	1787 (87.7%)
11	98.3 (8.0)	1568 (92.7%)	98.5 (7.3)	1748 (90.2%)	98.2 (8.2)	1767 (87.0%)
12	98.7 (6.2)	1494 (92.7%)	99.1 (5.3)	1721 (90.1%)	98.7 (7.5)	1724 (86.8%)
13	98.5 (7.7)	1488 (93.2%)	98.9 (6.4)	1719 (90.8%)	98.8 (7.1)	1726 (87.7%)
14	97.9 (9.3)	1472 (93.4%)	98.4 (7.3)	1693 (90.0%)	98.0 (9.1)	1711 (87.3%)
15	98.5 (6.9)	1394 (92.1%)	99.2 (4.6)	1668 (90.0%)	99.0 (6.0)	1678 (87.0%)
16	98.2 (8.7)	1372 (92.3%)	99.1 (4.6)	1657 (90.3%)	99.1 (5.7)	1674 (87.5%)
17	98.1 (9.8)	1360 (92.0%)	98.3 (7.8)	1633 (89.4%)	98.5 (6.4)	1662 (87.3%)
18	98.7 (6.8)	1276 (90.1%)	99.3 (4.1)	1574 (89.0%)	99.2 (5.3)	1602 (86.1%)
19	98.7 (7.3)	1270 (90.2%)	99.3 (3.8)	1563 (89.0%)	99.4 (3.1)	1605 (86.9%)
20	98.4 (8.9)	1260 (90.2%)	98.9 (5.3)	1546 (88.7%)	98.7 (5.8)	1590 (86.5%)
21	98.5 (7.5)	1145 (88.0%)	99.0 (6.1)	1458 (87.0%)	98.8 (7.1)	1516 (85.0%)
22	97.8 (9.7)	1106 (88.8%)	98.8 (6.2)	1431 (86.9%)	99.2 (5.7)	1498 (84.7%)
23	98.1 (8.8)	1056 (89.5%)	98.2 (8.5)	1377 (85.1%)	98.4 (8.0)	1460 (83.2%)
24	98.8 (7.2)	913 (84.1%)	99.0 (6.3)	1207 (82.2%)	98.9 (7.1)	1255 (77.5%)
25	98.8 (6.7)	851 (85.4%)	99.2 (5.2)	1157 (80.8%)	98.8 (7.1)	1222 (76.9%)
26	97.9 (11.2)	728 (86.2%)	99.1 (5.7)	1051 (74.6%)	98.6 (8.8)	1176 (74.5%)
PERSISTENCE						
Mean *Mos, SD*	16.5 (8.4)		19.2 (7.5)		19.6 (6.9)	
Median *Mos,*	20.4		23.6		23.7	
N	2194		2169		2135	

[a]Standard deviation

[b]Number of patients with drug diary data available

the number of patients who initiated each cycle declined over time from cycles 1 ($N=2290$) to 26 ($N=845$; data not shown), reflecting early discontinuation of palbociclib for protocol-defined toxicity and iDFS events. Within the same study arm, the mean proportion of patients who adhered to their daily ET ranged from 98.7 to 99.1% from cycle 1 to 26, with a similar decline in the number of patients who initiated each cycle seen over time.

Within the ET alone arm, the mean proportion of patients who adhered to their daily ET ranged from 99.0% at cycle 1 to 98.6% at cycle 26. The number of patients who initiated each cycle declined over time from $N=2343$ at cycle 1 to $N=1578$ at cycle 26 (data not shown). The drug diaries at cycles 1 through 26 were completed by ≥ 84% of the patients who initiated the corresponding cycle (Table 2).

Based on drug diaries ($N=2194$), the median time from initiation of palbociclib to cessation of palbociclib (irrespective of breaks in therapy) was 20.4 months, and the mean persistence was 16.5 months, with a standard deviation of 8.4 (Table 2). Results were similar based on the clinically captured pill counts ($N=2289$; median = 21.3 months, mean = 16.9; SD = 8.4; data not shown). Before being moved to long-term follow-up, the median persistence of endocrine therapy in the palbociclib + ET group was 23.6 months, and the mean was 19.2 months (SD = 7.5), with nearly identical numbers seen in the ET alone group (Table 2).

When the modified Morisky scale was used to measure patient-reported adherence to palbociclib, the proportion of patients who scored 5 out of a possible maximum score of 5 (i.e., most adherent) ranged from 79.6 to 75.5% from cycles 2 to 24. After adjusting for demographic and clinical covariates, the estimated marginal probability of achieving the most adherent score was 80% at cycle 2 and 75% at cycle 24 (Table 3). When the McHorney scale was used, the proportion of patients who scored 0 out of a possible score of 36 (most adherent) ranged from 64.0% at cycle 2 to 73.4% at cycle 24. After adjustment for clinical-demographic factors, the estimated marginal probabilities ranged from 64 to 72% (Table 3).

When comparing the proportion of patients who were maximally adherent to ET between arms across all timepoints, the marginal probability of maximal adherence was significantly higher in the palbociclib + ET group, compared to ET alone, whether using the modified Morisky ($p<0.0001$; Fig. 1) or the McHorney ($p=0.05$; Fig. 2). However, the interaction term for group by cycle was not significant, regardless of self-report measure used ($p=0.42$ Morisky; $p=0.14$ McHorney), indicating that the pattern of change for those reporting being most adherent was not significantly different between groups.

Lastly, when using either study diary or pill count data to measure palbociclib daily adherence, no statistically significant iDFS hazard reduction was observed after the 6 month landmark when comparing patients who were < 90% versus ≥ 90% adherent (Fig. 3). Daily adherence to palbociclib refers to adherence within each study cycle and is not to be confused with persistence to palbociclib, whose impact on iDFS was reported previously [15]. Rather than the traditional 80% cutoff, we used a 90% cutoff since there were very few patients who reported < 80% adherence after the 6-month landmark for either study diary or pill count. The 6 month landmark was chosen since > 80% of the patient population was still providing palbociclib diary data and since few events occurred after the 12 month landmark.

Adherence calculated from palbociclib pill counts from clinical database. All available adherence information up to the 6 month landmark time point was used to create the adherence groupings (cycles with missing pill counts prior to the landmark time point were ignored). Total palbociclib adherence over the first 6 cycles for the landmark time

Table 3 Percentage and predicted probability of maximal adherence to palbociclib, via Morisky composite and McHorney

Morisky composite scale[a]				McHorney brief adherence estimator		
Cycle	Percent "most adherent" (score = 5) (%)	Probability [95% CI][b] (adjusted for key baseline factors)	*N*	Percent "most adherent" (score = 0) (%)	Probability [95% CI][b] (adjusted for key baseline factors)	*N*
2	79.6	0.80 [0.78, 0.81]	1773	64.0	0.64 [0.61, 0.67]	873
3	78.6	0.79 [0.77, 0.81]	1781	67.2	0.67 [0.64, 0.70]	877
6	72.0	0.72 [0.70, 0.74]	1744	66.9	0.66 [0.63, 0.69]	838
12	71.9	0.71 [0.69, 0.74]	1511	67.2	0.66 [0.63, 0.70]	729
18	74.9	0.74 [0.72, 0.76]	1280	67.2	0.66 [0.62, 0.69]	610
24	75.5	0.75 [0.72, 0.77]	942	73.4	0.72 [0.68, 0.76]	444

Morisky Composite scores range from 0 to 5 with a score of 0 indicating "least adherent" and a score of 5 indicating "most adherent." McHorney scores range from 0 to 36 with zero indicating lowest risk for intentional nonadherence

[a]Composite Morisky = MMAS-4 + whether the doctor's instructions for palbociclib/ET were followed exactly

[b]95% Confidence Interval after adjusting for age category, first adjuvant ET, race, ethnicity, N-stage, T-stage, PgR, prior chemotherapy, baseline ECOG

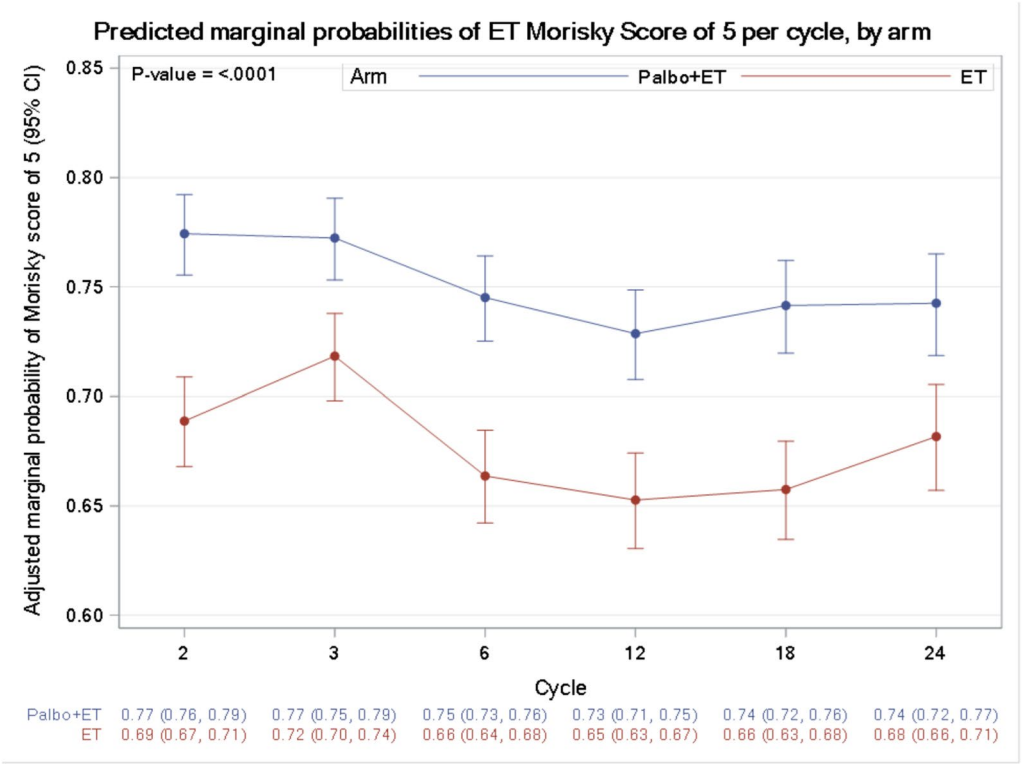

Fig.1 Predicted probability of most adherent to endocrine therapy (ET) via Morisky composite, by arm

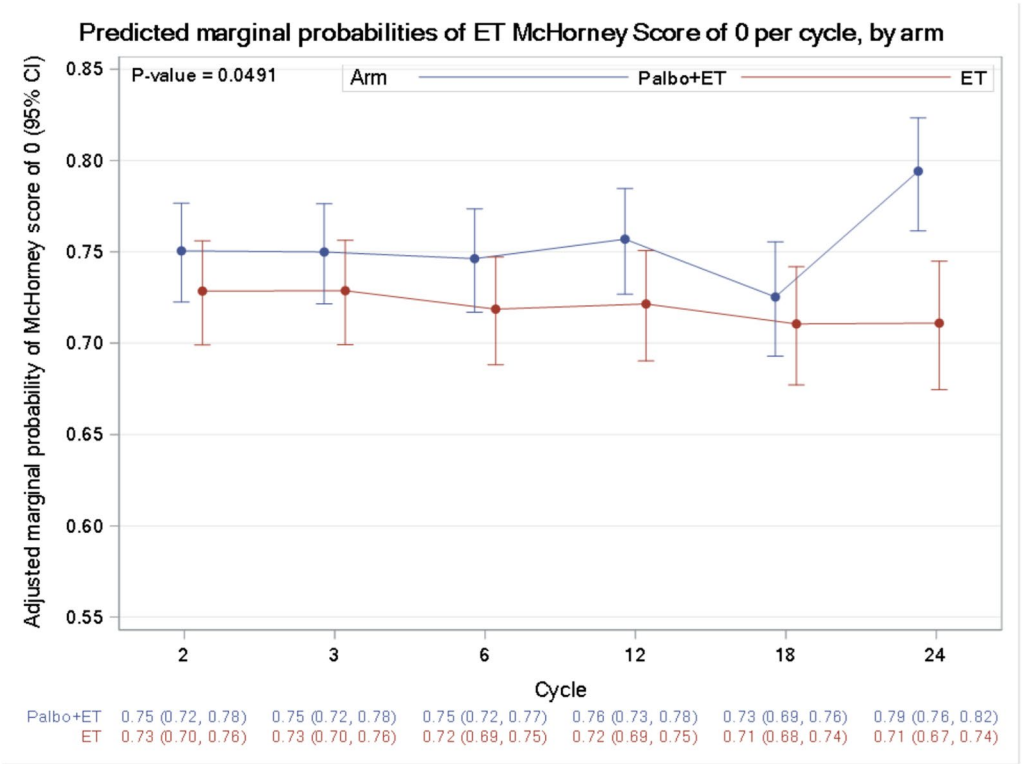

Fig. 2 Predicted probability of being most adherent to endocrine therapy (ET) via McHorney, by arm

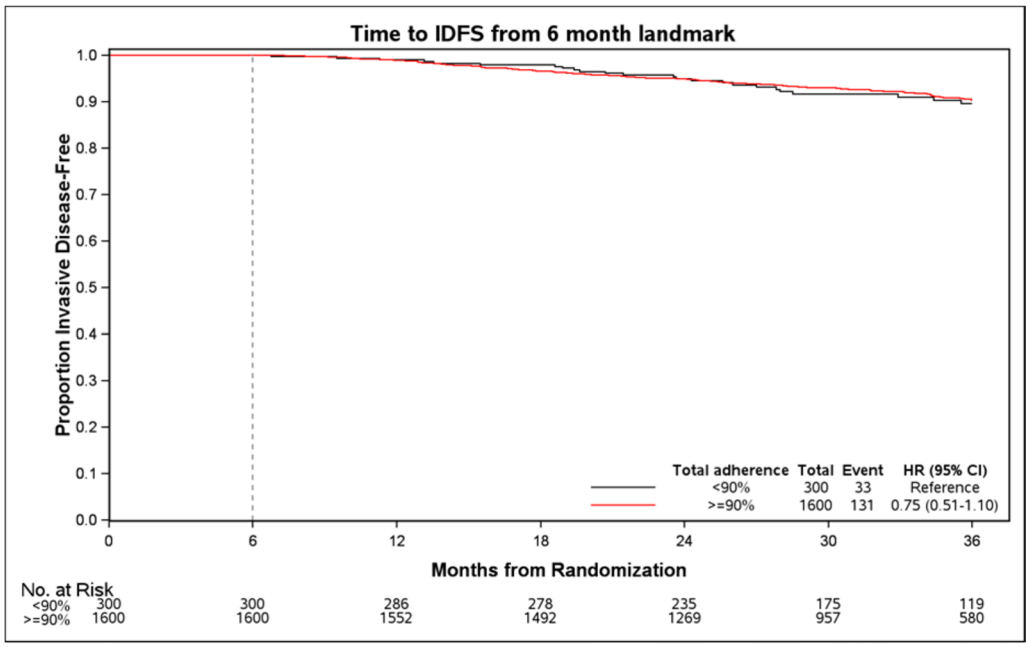

Fig. 3 Daily palbociclib adherence as measured by pill count and time to invasive disease-free survival (iDFS) from 6-month landmark

point 6 months was used to determine the groups. Includes patients who are event-free and still receiving palbociclib at the landmark time point.

Discussion

The addition of the oral CDK 4/6 inhibitor palbociclib to ongoing daily adjuvant ET did not appear to negatively impact PALLAS participants' adherence to ET. When measured with study diary, patients randomized to palbociclib + ET had virtually identical levels of daily ET adherence as the ET alone group. When measured across all time points with patient-reported adherence measures, patients randomized to palbociclib + ET were significantly more likely to report a pattern of maximal adherence scores compared to patients in the ET alone group. The findings in this analysis counter a longstanding concern that managing multiple medication regimens and toxicity profiles will reduce patient adherence, which may be reassuring to clinicians considering the use of targeted therapies in combination with ET [1].

Given the potential threat to external validity, robust measurement of participant adherence to long-term self-administration of investigational drugs is critical. However, adherence to oral study drug is reported in only 20–46% of randomized clinical trials [19–21]. (8) This lack of contextual information hinders research interpretation for clinicians prescribing long-term oral anticancer therapies in real-world settings [22], especially since racial, ethnic, and income disparities in adherence to adjuvant ET have been well-documented [23–26].

Levels of maximal adherence to ET and to palbociclib were consistently lower when measured with the self-report Morisky and McHorney questionnaires compared to levels measured by study diary and pill count. It is possible that meeting study staff in person to submit study diaries and pill bottles engendered more social desirability bias compared to completing a brief, neutrally worded questionnaire [27, 28]. Closer examination of the McHorney scale questions, which assess patient beliefs about the drug's necessity, cost–benefit ratio, and affordability, suggest that the scale was measuring different aspects of adherence beyond pill-taking behavior itself. Considering the disparate adherence values obtained via PRO measures versus pill count/diary, it is recommended that validated patient-reported adherence measures be included whenever possible [29].

An earlier analysis of the PALLAS data found no statistically significant impact of early discontinuation of palbociclib during the 2 year treatment period and 3 year iDFS [15]. We used all available adherence information up to 10 landmark times (1, 2, 3, 6, 9, 12, 15, 18, 21, 24 months) to create the adherence groupings. The exploratory landmark analyses largely confirmed that patient nonadherence to palbociclib was not a major contributor to the lack of iDFS benefit seen in the overall PALLAS trial. In contrast, the phase 3 study MonarchE demonstrated improved survival outcomes for the addition of 2 years of the CDK4/6 inhibitor abemaciclib to ongoing adjuvant ET compared with ET alone. (14) In this trial, 25.8% of patients discontinued abemaciclib early [30].

Similarly, a first presentation from the phase 3 NATALEE study (NCT03701334) [31], a trial of similar design using a 3 year course of lower dose ribociclib, has reported iDFS benefits; further follow-up is necessary to determine whether using a lower dose improves rates of early discontinuation.

Limitations

It is possible that adherence was measured more crudely for ET than palbociclib, as measures for ET were limited to diary alone since ET was obtained commercially and not distributed by the study. However, it is unlikely that a large difference in adherence to ET was missed by not having pill count data available. Additionally, daily adherence measures for ET were limited to those patients with completed diaries for each cycle. Therefore, these values may be misleadingly high. For example, in the palbociclib + ET group, the number of patients who initiated each cycle declined from $N = 2290$ at cycle 1 to $N = 1086$ at cycle 24. Therefore, while the adherence data gathered for each cycle was representative and missing data were kept to a minimum, it did not include patients who had stopped taking their medication, although it should be emphasized that the majority of early discontinuation was protocol-defined for toxicity or iDFS events. Similarly, the decline in patient numbers impacted the reliability of the landmark analysis, given that those who were event-free and remained on study drug decreased from $N = 2135$ at month 1 to $N = 1517$ at month 12 and $N = 724$ at month 24 (data not shown). Finally, the landmark analyses results should be interpreted with caution as the comparison was made between patients who had very high adherence ($\geq 90\%$) vs those with lower adherence ($< 90\%$) still receiving study drug treatment.

Conclusion

The addition of the CDK 4/6 inhibitor palbociclib did not appear to negatively impact patient adherence to ongoing adjuvant ET in the Pallas trial. For patients who remained on study treatment, within-cycle daily adherence rates for palbociclib + ET and ET alone were consistently high across all cycles. Mean persistence was also strikingly high with ET, and to a slightly lesser degree with palbociclib. PRO measures detected sizably lower levels of optimal adherence for palbociclib + ET or ET alone. These results illustrate the importance of carefully measuring and monitoring adherence in studies that entail patient administration of oral study agents.

Acknowledgements Research reported in this publication was supported in part by the Alliance Foundation Trials, LLC (AFT-05); https://acknowledgments.alliancefound_org); also in part by funds from the Austrian Breast and Colorectal Cancer Study Group (ABCSG-42), in cooperation with PrECOG, BIG, GBG, and NSABP. This research is supported by Pfizer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Alliance Foundation Trials, LLC. Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Numbers U10CA180821 and U10CA180882 (to the Alliance for Clinical Trials in Oncology). This data were presented at SABC 2021.

Author contributions ES, AHP, ELM, DZ, DH, CF, AZ, ACW, HB, CS, AD, and MG conceived the study and design. AD, NZ, JL, JM, VB-R, MN, GP, KG, JMB, DE, GZ, TT, MMJ, SAN, TH, AC, AR, JJPL, DS, HJB, ZIN, GP-T, AB, MB-E, TF, YN, GR, CS, KM, OM, TG, AHP, LAC, ELM and MG were involved in patient recruitment, data collection and data curation. DZ, AZ, DH, and CF analyzed the data. ES, AHP, ELM, NZ, MN and DZ wrote the manuscript. ELM and MG contributed equally to this work as last authors. All authors were involved in writing, reviewing and editing the original draft. All authors approved the final manuscript.

Funding Funding was provided by Alliance Foundation Trials (Grant No. AFT-05, PrECOG), Austrian Breast and Colorectal Cancer Study Group (Grant No. ABCSG-42).

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests ADM reports institutional research support from Pfizer (Inst), Genetech (Inst), Novartis (Inst), NeoGenomics (Inst); honoraria from Fox Chase Cancer Center SABCS review 2024, Fox Chase Cancer Center SABCS review 2023, 3rd Annual Perspectives in Breast Cancer Care-Medscape 2023, 21st Annual International Congress on the Future of Breast Cancer® West San Deigo 2022, OncLive Institutional Perspectives in Cancer: Breast Cancer 2022, University Of Kanas City Post San Antonio Review 2022, ASCO 2021 Breast Cancer Highlights 2021. NZ reports honoraria from Lilly, Gilead, Pfizer, Eisai, AstraZeneca, Novartis; travel support for educational meeting attendance from Pfizer, Lilly and Novartis; participation on Advisory board for DMC; leadership for Scientific Advisory Committee Chair. JLreports honoraria from Novartis, Eli Lilly, Merck, Astra Zeneca, Daiichi Sanko, Exact Science, Gilead. GP reports research funding from Amgen, Roche,Accord, Lilly, Novartis, Seagen, Gilead, Daiichi, Menarini, Pfizer, MSD, Merck; honoraria from Amgen, Roche, Accord, Pfizer, Lilly, Merck, Daiichi, Menarini, Novartis, Seagen, MSD, and Gilead; consulting for Pfizer, Amgen, Lilly, Novartis, Merck, Daiichi, Roche, Gilead, MSD, Menarini, and Seagen; payment for expert testimony from Amgen, Roche,Accord, Lilly, Novartis, Seagen, Gilead, Daiichi, Menarini, Pfizer, MSD, Merck; travel support from Amgen, Roche,Accord, Lilly, Novartis, Seagen, Gilead, Daiichi, Menarini, Pfizer, MSD, Merck. KG reports honoraria from Eli Lilly, Pfizer, Novartis; participation in an advisory board for Eli Lilly, Pfizer, Novartis. DE reports honoraria from AstraZeneca, Daiichi-Sankyo, Gilead, Lilly, MSD, Menarini, Novartis, Pfizer, Roche, Seagen, Sirius Medical; Support for attending meetings/travel from AstraZeneca, Daiichi-Sankyo, Pfizer, Roche; participation on an advisory board for AstraZeneca, Daiichi-Sankyo, Gilead, Lilly, MSD, Menarini, Novartis, Pfizer, Roche, Seagen, Sirius Medical. GZ reports a leadership role in Immunomica S.r.l. TT reports research funding from Pfizer, AstraZeneca, Astellas Pharma, Genentech/Roche, Daiichi Sankyo, and Ayala Pharmaceuticals; consulting fees from Genentech/Roche, Pfizer, AstraZeneca, Merck, Daiichi Sankyo, Gilead Sciences, Novartis, GlaxoS-

mithKline, GE Healthcare, bioTheranostics, Hengrui Pharmaceuticals, G1 Therapeutics, Tersera, Stemline Therapeutics, Exact Sciences; participation on an advisory board for Genentech/Roche, I-SPY; and leadership for ASCO Breast Cancer Guideline Advisory Group (Co-Chair) and Chemo Foundation Symposium (Co-Chair). MMJ reports consulting fees from AstraZeneca, Lilly, MSD, Novartis, and Pfizer; honoraria from AstraZeneca, MSD, and Lilly. TH reports research funding from Takeda Onocolgy and consulting for Puma Biotechnology (Inst). AC reports honoraria from Olema Steering Committee; support for attendance/travel from San Antonio Breast Cancer Symposium by Olema; and leadership as Vice Chair for Breast Cancer Research Centre. AER reports consulting fees from Lilly, Seagen, and Gilead; honoraria from Pfizer, Lilly, Novartis, AZ/Daiichi-Sankyo, MSD, and Zuellig Pharma. AW reports research funding from Genentech (Inst), Merck Sharp & Dohme (Inst), Array BioPharma (Inst); he has been named as inventor on one or more issued patents or pending patent applications relating to methylation in breast cancer, and has assigned his rights to Johns Hopkins University (JHU), and participates in a royalty sharing agreement with JHU. WFS reports patent planned/issued/pending for genomic predictor of sensitivity to endocrine therapy for breast cancer and stock in Delphi Diagnostics. JJPL reports honoraria from Seattle Genetics, Novartis, Pfizer, AstraZeneca/ Daiichi Sankyo, Lilly, and Roche; advisory roles with Seattle Genetics, Novartis, AstraZeneca/ Daiichi Sankyo, Pierre Fabre, and Roche. DS reports honoraria from MSD, AZ, Gilead; participation on a Data Safety Monitoring Board for MSD. AB reports consulting fees from Astrazeneca, Pfizer, Novartis, Lilly, Genentech/Roche, SeaGen, Daiichi Sankyo, Merck, Agendia, Sanofi, Puma, Myriad, Gilead. MB-E reports personal fees from Pfizer, Novartis, and Lilly, outside the submitted work; and travel expenses from Pfizer and Roche. TF reports research support from Pfizer (Inst), AstraZeneca (Inst), Novartis (Inst), and Veracyte; royalties/licenses from UpToDate; consulting fees from Affibody; honoraria from Gilead, Pfizer, Roche, AstraZeneca; receipt for equipment/material/drugs/i.e. from AstraZeneca, Novartis, Veracyte, and Pfizer. YN reports honoraria from Novartis, Radius/Stemline, Astellas. GR reports consulting fees from Roche, Lilly, Pfizer, Novartis, Swixx, and AstraZeneca; honoraria from Novartis and Roche; support for attending meetings/travel from Swizz, Pfizer, and Roche. CFS reports grants and honoraria by Amgen, Daiichi Sankyo, Eli Lilly, Novartis, AstraZeneca, Pfizer, Roche, Seagen, Gilead, MSD. KM reports funding of study and partial support of salary from Pfizer. OM reports research funding from Pfizer; consulting fees from Grupo Oncoclinicas (Brazil); honoraria from Astra Zeneca, Merck, and Sanofi. TG reports research support from Pfizer. EL is employed by and a stockholder of Pfizer. AHP reports royalties from UpToDate Royalties. LAC reports other uncompensated financial/nonfinancial interests from Lilly, Seattle Genetics, Novartis, Genentech/Roche, and GSK. DH reports funding of study and partial support of salary from Pfizer. CF reports funding of study and partial support of salary from Pfizer. ELM reports a consulting role with Lilly, Novartis, AstraZeneca and Gilead. MG reports funding of study from Pfizer; consulting fees from EPG Health and MSD; honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Menarini, Novartis, Pierre Fabre; payment for expert testimony from Eli Lilly and Veracyte; non-paid participation on an advisory board for ATNEC trial; and leadership in ABCSG. The remaining authors declare no competing interests.

Ethical approval This study was conducted in line with the principles of the Declaration of Helsinki. The research protocol was approved by local or central institutional boards or ethics committees. The trial was monitored throughout by an international independent data monitoring committee. Patients provided written informed consent before participating in the study.

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