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ORIGINAL RESEARCH

Palbociclib combined with endocrine treatment in hormone receptor-positive, HER2-negative breast cancer patients with high relapse risk after neoadjuvant chemotherapy: subgroup analyses of premenopausal patients in PENELOPE-B☆

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Background: The PENELOPE-B study demonstrated that the addition of 1-year post-neoadjuvant palbociclib to endocrine therapy (ET) in patients with high-risk early breast cancer (BC) did not improve invasive disease-free survival (iDFS) compared to placebo. Here, we report results for premenopausal women.

Patients and methods: Patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative BC at high risk of relapse [defined as no pathological complete response after neoadjuvant chemotherapy and a clinical, pathological stage, estrogen receptor, grading (CPS-EG) score $\geq$3 or 2/ypN+] were randomized to receive 13 cycles of palbociclib or placebo + standard ET. Ovarian function (OF) was evaluated by centrally assessed estradiol, follicle-stimulating hormone and anti-Müllerian hormone serum levels.

Results: Overall, 616 of 1250 randomized patients were premenopausal; of these, 30.0% were <40 years of age, 47.4% had four or more metastatic lymph nodes, and 58.2% had a CPS-EG score $\geq$3. 66.1% of patients were treated with tamoxifen alone, and 32.9% received ovarian function suppression (OFS) in addition to either tamoxifen or aromatase inhibitor (AI). After a median follow-up of 42.8 months (97.2% completeness) no difference in iDFS between palbociclib and placebo was observed [hazard ratio = 0.95, 95% confidence interval (CI) 0.69-1.30, $P = 0.737$]. The estimated 3-year iDFS rate was marginally higher in the palbociclib arm (80.6% versus 78.3%). Three year iDFS was higher in patients receiving AI than tamoxifen plus OFS or tamoxifen alone (86.0% versus 78.6% versus 78.0%). Patients receiving tamoxifen plus OFS showed a favorable iDFS with palbociclib (83.0% versus 74.1%, hazard ratio = 0.52, 95% CI 0.27-1.02, $P = 0.057$). Hematologic adverse events were more frequent with palbociclib (76.1% versus 1.9% grade 3-4, $P < 0.001$). Palbociclib seems not to negatively impact the OF throughout the treatment period.

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Conclusions: In premenopausal women, who received tamoxifen plus OFS as ET, the addition of palbociclib to ET results in a favorable iDFS. The safety profile seems favorable and in contrast to chemotherapy palbociclib does not impact OF throughout the treatment period.

Key words: early breast cancer, hormone receptor positive, HER2 negative, adjuvant CDK4/6 inhibitor, palbociclib, premenopausal, PENELOPE-B, ovarian function

INTRODUCTION

Premenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) early breast cancer (BC) at low risk of recurrence are adequately treated with tamoxifen alone.[1,2] Several strategies to improve outcomes have been investigated for premenopausal patients at higher risk of recurrence, including the addition of ovarian function suppression (OFS) in combination with either tamoxifen or an aromatase inhibitor (AI). The selection of patients who will benefit most from treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is challenging. Potential benefits must be weighed against additional symptom burden resulting from the use of OFS and AIs.[1,3,4] Patients younger than 35 years have the largest absolute benefit from adding OFS and especially AIs, but non-adherence to OFS is significantly higher compared to their older counterparts.[4] Underlying reasons include toxicity, a desire of pregnancy and the need for monthly OFS administration.[4-7] Increasing the efficacy of adjuvant endocrine therapy (ET) without increasing menopausal and musculoskeletal symptoms in this age group remains an important strategy to increase adherence and improve outcomes.[8]

CDK4/6i have consistently shown to improve progression-free survival in metastatic HR+, HER2− BC, whilst maintaining quality of life, including in premenopausal patients.[9,10] This has prompted the investigation of CDK4/6i as adjuvant therapy. So far, four large trials have reported inconsistent results.[11-14] The monarchE trial showed that the addition of 2 years of abemaciclib to adjuvant ET in patients with high-risk HR+, HER2− BC led to a significant improvement of invasive disease-free survival (iDFS), which was maintained throughout a median follow-up (FU) of 27 months.[11,15,16] After a pronounced effect of premenopausal patients further analyses in this cohort revealed an absolute improvement at 3 years of 5.7% for iDFS and 4.4% for distant relapse-free survival rates.[17] In PENELOPE-B, 13 cycles of post-neoadjuvant palbociclib did not significantly improve iDFS when added to ET. However, a transient numerical improvement in iDFS was observed through 3 years.[12] A prolonged duration of palbociclib therapy for 2 years in the PALLAS trial again did not show any benefit in terms of iDFS.[13] The NATALEE trial has recently reported an absolute iDFS benefit of 3.3% from adding 3 years of ribociclib to an AI [hazard ratio = 0.75, 95% confidence interval (CI) 0.665-0.91, $P = 0.001$].[14] Differences in study design, patient selection, duration of treatment and FU might explain the contrasting results.

The impact of therapeutic interventions on ovarian function (OF) is rarely assessed in early BC trials, although these results are needed for fertility counseling in clinical practice. No trials investigating CDK4/6i have reported prespecified OF endpoints.[18] The consequences of ET, including premature menopause, impaired family planning, lifestyle and sexual health, in premenopausal patients have distinct medical and psychosocial implications and mandate a special focus on premenopausal patients within large clinical trials.

Here, we report an analysis of premenopausal patients treated within the post-neoadjuvant PENELOPE-B trial, including a prospective evaluation of OFS throughout the treatment period.

Patients and methods

This exploratory subgroup analysis included premenopausal women treated within the PENELOPE-B (NCT01864746) trial. PENELOPE-B is a prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, phase III study investigating the addition of 1 year of palbociclib to standard adjuvant ET in patients with HR+/HER2− early BC with residual invasive disease after standard neoadjuvant chemotherapy (NACT) and high risk of relapse defined as a clinical, pathological stage, estrogen receptor, grading (CPS-EG) score of ≥3 or 2 with ypN+.[19,20] ET with either tamoxifen or an AI with or without OFS was given according to local guidelines for a minimum duration of 5 years and could have been started before the enrollment into the study. Estrogen receptor (ER) and progesterone receptor positivity was centrally assessed and defined as ≥1% positively stained cells and HER2 negativity as an immunohistochemistry score of 0-1 or fluorescence *in situ* hybridization test ratio <2.0. Details on the PENELOPE-B trial and primary results have been previously published.[12] This analysis was based on the menopausal status reported by the investigator.

Objectives and endpoints

We report iDFS in premenopausal patients stratified by study treatment and type of ET. iDFS was defined as the time in months between randomization and first event including ipsilateral invasive in-breast or locoregional recurrence, invasive contralateral BC, distant recurrence, second primary invasive (non-breast) cancer or death of any cause.[21] Safety was analyzed in all randomized patients.

Additionally, we assessed the impact of palbociclib on OF. Estradiol (E2), follicle-stimulating hormone (FSH) and the anti-Müllerian hormone (AMH) were centrally assessed in serum samples collected at baseline, before cycle (C) 7 and at the end of treatment (EOT, 30 days after

last intake of study drug). FSH >12.4 IU/l and E2 <52.2 ng/l were defined as postmenopausal hormone levels; fertile levels of AMH were defined as ≥0.22 ng/ml.[22] Patients were defined as pre- or postmenopausal in compliance with the current local guidelines (last menstrual period >12 months at study entry before receiving chemotherapy). The median level of FSH, E2 and AMH, the rate of pre- versus postmenopausal hormone levels and fertile versus non-fertile AMH levels were compared between treatment arms at baseline, before C7 and at EOT. Subgroup analyses were carried out in patients with pre- versus postmenopausal FSH/E2 levels at baseline, according to age <40 versus ≥40 years and the use of OFS (yes versus no) during the trial.

Statistical analysis

The Kaplan–Meier method was used to estimate the survival probability at specific time points together with a two-sided 95% CI; univariate Cox proportional hazards models were used to calculate hazard ratios with two-sided 95% CIs. Survival probabilities were compared using the log-rank test and/or Wald *P* value from Cox regressions. To test interaction between subgroups and treatment, Cox models including subgroup variable, treatment and their interaction were used. The safety population consists of all patients receiving at least one dose of study treatment. Fisher's exact test was used to compare rates of all-grade as well as grade (G) 3-4 adverse events (AEs). Rates (rate of pre-/postmenopausal hormone levels, AMH fertile/non-fertile

Table 1. Baseline characteristics

Parameter	Category	Palbociclib *n* = 300 *n* (valid %)	Placebo *n* = 316 *n* (valid %)	Overall *n* = 616 *n* (valid %)	*P* value
Age, years	Median (min, max)	43.0 (22.0, 55.0)	43.0 (19.0, 56.0)	43.0 (19.0, 56.0)	0.589
	<30	11 (3.7)	14 (4.4)	25 (4.1)	0.799
	30 to <40	83 (27.7)	77 (24.4)	160 (26.0)	
	40 to <50	176 (58.7)	192 (60.8)	368 (59.7)	
	50 to <60	30 (10.0)	33 (10.4)	63 (10.2)	
ECOG performance status	ECOG 0	259 (86.3)	273 (86.4)	532 (86.4)	0.983
	ECOG 1	41 (13.7)	43 (13.6)	84 (13.6)	
Tumor focality by sonography	Unifocal	192 (66.2)	187 (61.5)	379 (63.8)	0.412
	Multifocal	65 (22.4)	73 (24.0)	138 (23.2)	
	Multicentric	33 (11.4)	44 (14.5)	77 (13.0)	
Clinical tumor stage by sonography	cT1	14 (4.7)	28 (8.9)	42 (6.8)	0.207
	cT2	150 (50.2)	154 (48.9)	304 (49.5)	
	cT3	101 (33.8)	96 (30.5)	197 (32.1)	
	cT4	34 (11.4)	37 (11.7)	71 (11.6)	
Histological tumor stage at surgery	ypT0	13 (4.3)	6 (1.9)	19 (3.1)	0.163
	ypTis	1 (0.3)	2 (0.6)	3 (0.5)	
	ypT1	103 (34.3)	103 (32.7)	206 (33.5)	
	ypT2	115 (38.3)	148 (47.0)	263 (42.8)	
	ypT3	60 (20.0)	50 (15.9)	110 (17.9)	
	ypT4	8 (2.7)	6 (1.9)	14 (2.3)	
Clinical nodal status by sonography	cN0	23 (7.7)	36 (11.4)	59 (9.6)	0.253
	cN1	221 (73.7)	211 (66.8)	432 (70.1)	
	cN2	33 (11.0)	42 (13.3)	75 (12.2)	
	cN3	23 (7.7)	27 (8.5)	50 (8.1)	
Histological nodal status at surgery	ypN0	13 (4.4)	16 (5.1)	29 (4.8)	0.941
	ypN1	140 (47.1)	152 (48.6)	292 (47.9)	
	ypN2	110 (37.0)	110 (35.1)	220 (36.1)	
	ypN3	34 (11.4)	35 (11.2)	69 (11.3)	
Tumor grading, local (core biopsy)	G1	19 (6.4)	24 (7.7)	43 (7.1)	0.228
	G2	171 (57.6)	158 (50.6)	329 (54.0)	
	G3	107 (36.0)	130 (41.7)	237 (38.9)	
Histological tumor type	Ductal or ductal–lobular invasive	263 (87.7)	286 (90.5)	549 (89.1)	0.272
	Lobular invasive carcinoma	24 (8.0)	24 (7.6)	48 (7.8)	
	Mucinous carcinoma	4 (1.3)	2 (0.6)	6 (1.0)	
	Invasive micropapillary carcinoma	1 (0.3)	2 (0.6)	3 (0.5)	
	Other	8 (2.7)	2 (0.6)	10 (1.6)	
Histological lymph node status at surgery documented at randomization	ypN 0-1	156 (52.0)	168 (53.2)	324 (52.6)	0.809
	ypN 2-3	144 (48.0)	148 (46.8)	292 (47.4)	
Ki-67% centrally at randomization[a]	≤15%	229 (76.3)	245 (77.5)	474 (76.9)	0.774
	>15%	71 (23.7)	71 (22.5)	142 (23.1)	
Global region of participating site	Non-Asian	268 (89.3)	288 (91.1)	556 (90.3)	0.498
	Asian	32 (10.7)	28 (8.9)	60 (9.7)	
Risk status	CPS-EG score 2 and ypN+	124 (41.3)	138 (43.7)	262 (42.5)	0.569
	CPS-EG score ≥3	176 (58.7%)	178 (56.3)	354 (57.5)	

AI, aromatase inhibitor; CPS-EG, clinical, pathological stage, estrogen receptor, grading; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine treatment; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat.
[a]Central pathology, preferably based on surgical tissue and if not available based on biopsy.

levels) were reported per time point/subgroup in frequency tables with number and percent of patients in each category; rates were compared using Fisher's exact test. The statistical analysis is exploratory. All reported *P* values are two-sided and to be considered descriptive. CIs symmetrically span 95%. Adjustment for multiple testing was not planned or carried out.

RESULTS

Patients and treatment

In PENELOPE-B, 1250 patients were randomized to either palbociclib or placebo in addition to ET. Overall, 616 patients (49.3%) were defined as premenopausal after surgery before enrollment into PENELOPE-B. Baseline characteristics of premenopausal patients were well balanced between the treatment arms (Table 1). In this cohort, median age at diagnosis was 43 years (range 19-56 years); 25 of 616 (4.1%) patients were aged <30 years, 160 of 616 (26.0%) 30-39 years, 368 of 616 (59.7%) 40-49 years and 63 of 616 (10.2%) ≥50 years. 57.5% were included with a CPS-EG score ≥3 and 47.4% had ≥4 metastatic axillary lymph nodes at surgery.

Overall, 99.2% of the premenopausal patients were treated with anthracycline- and taxane-based NACT and 98.2% received adjuvant radiotherapy. Tamoxifen alone was used in 66.1% and OFS in 32.9% of the patients as part of their initial ET, together with tamoxifen in 19.3%, and an AI in 13.6% of the patients. 4.5% of the patients started OFS during study treatment (Table 2). Separated by age, the rate of OFS together with tamoxifen was 32.4% in patients aged <40 years and 13.7% in patients aged ≥40 years ($P < 0.001$). In comparison, the rate of OFS together with AI was 17.8% in patients aged <40 years and 11.8% in patients aged ≥40 years ($P < 0.055$). The rate of OFS varied significantly by age and was 50.3% in patients aged <40 years, but only 25.5% in patients aged ≥40 years ($P < 0.001$). In the age group <35 years, OFS was used in 65.4% as part of the initial ET (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103466). Only 32 (5.2%) of the premenopausal patients switched ET during the trial, most of them from tamoxifen to an AI (25 patients) and 2 patients from an AI to tamoxifen.

Efficacy

After a median FU of 42.8 months (97.2% completeness), 157 iDFS events (25.5%) have been documented in premenopausal patients, mainly distant recurrences (74.5%). There was no significant difference in iDFS between the treatment arms (hazard ratio = 0.95, 95% CI 0.69-1.30, $P = 0.737$; Figure 1A). The estimated 3-year iDFS rate was 80.6% (95% CI 75.5% to 84.8%) in the palbociclib arm and 78.3% (95% CI 73.1% to 82.5%) in the placebo arm (Figure 1A).

The 3-year iDFS rate in premenopausal patients receiving an AI + OFS as initial ET was 86.0% compared with 78.6% in patients receiving tamoxifen + OFS (hazard ratio = 1.48, 95% CI 0.79-2.75) and 78.0% in patients treated with tamoxifen alone (hazard ratio = 1.34, 95% CI 0.77-2.35, $P = 0.463$; Figure 1B), irrespective of the addition of palbociclib. A numerically favorable 3-year iDFS was observed for patients receiving palbociclib compared to placebo in addition to tamoxifen + OFS (83.0% versus 74.1%, hazard ratio = 0.52, 95% CI 0.27-1.02, $P = 0.053$; Figure 2). A test for interaction between type of ET and study treatment arm was not significant ($P = 0.124$).

Safety

All patients except one in each treatment arm experienced at least one AE. G3-4 AEs were significantly more frequent in the palbociclib arm compared to the placebo arm (81.1% versus 18.5%, $P < 0.001$), especially G3-4 hematologic AEs (76.1% versus 1.9%, $P < 0.001$; G1-4 99.0% versus 83.8%, $P < 0.001$; Table 3). Non-hematologic AEs did not differ significantly between treatment arms (G3-4 18.9% versus 16.6%, $P = 0.461$; G1-4 99.3% versus 99.4%, $P = 1.000$).

Table 2. Endocrine treatment

Parameter	Category	Palbociclib *N* = 300 *n* (valid %)	Placebo *N* = 316 *n* (valid %)	Overall *N* = 616 *n* (valid %)	*P* value
Start of ET	Before palbociclib/placebo	272 (90.7)	286 (90.5)	558 (90.6)	1.000
	Concomitantly with palbociclib/placebo	28 (9.3)	30 (9.5)	58 (9.4)	
First ET	Tamoxifen alone	199 (66.3)	208 (66.8)	407 (66.1)	0.932
	Tamoxifen plus OFS	61 (20.3)	58 (18.4)	119 (19.3)	0.542
	AI plus OFS	37 (12.3)	47 (14.9)	84 (13.6)	0.411
	Letrozole plus OFS	18 (6.0)	20 (6.3)	38 (6.2)	
	Exemestane plus OFS	15 (5.0)	20 (6.3)	35 (5.7)	
	Anastrozole plus OFS	4 (1.3)	7 (2.2)	11 (1.8)	
	AI alone[a]	3	3	6	1.000
OFS		98 (32.7)	105 (33.2)	203 (33.0)	
Type of OFS	Goserelin	90 (30.0)	94 (29.7)	184 (29.9)	
	Other GnRHa	7 (2.3)	11 (3.5)	18 (2.9)	
	Surgical	1	0	1	
	Radiologic	0	0	0	
Start of GnRHa during study therapy		11 (3.7)	17 (5.4)	28 (4.5)	

Type of first ET in premenopausal patients.
AI, aromatase inhibitor; ET, endocrine therapy; GnRHa, gonadotropin-releasing hormone analogue; OFS, ovarian function suppression.
[a]Patients receiving AI alone and were excluded from analyses according to ET treatment.

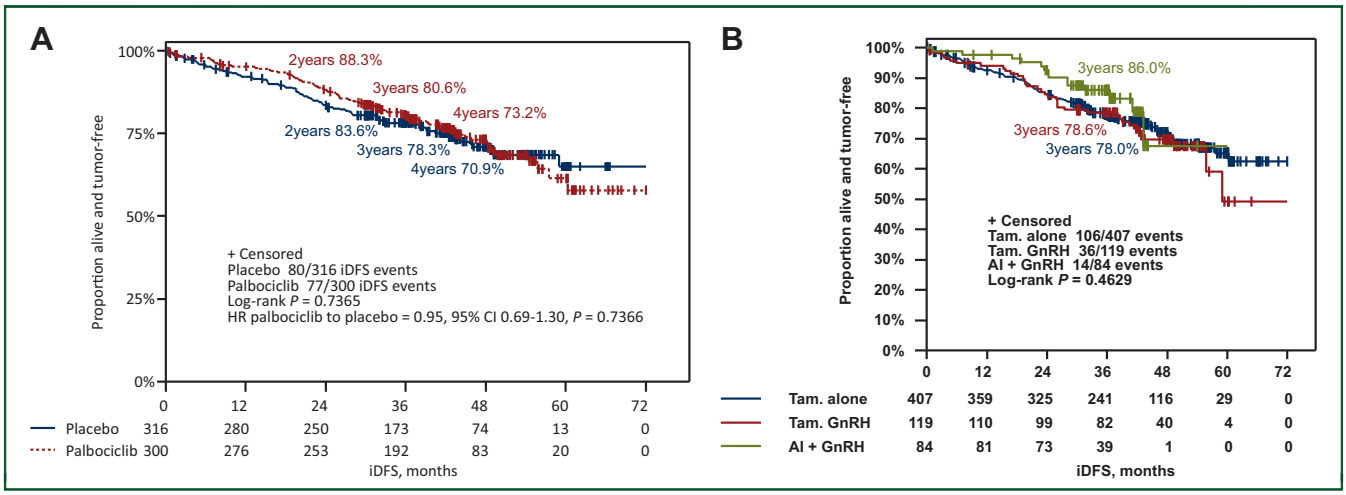

Figure 1. Kaplan–Meier curves for iDFS in premenopausal patients. Kaplan–Meier estimates for iDFS in premenopausal patients (A) according to treatment arm and (B) by endocrine treatment backbone.

AI, aromatase inhibitor; CI, confidence interval; GnRH, gonadotropin-releasing hormone; HR, hazard ratio; iDFS, invasive disease-free survival; Tam., tamoxifen.

More patients in the palbociclib arm experienced G1-4 hypocalcemia (43.9% versus 33.1%, $P = 0.008$), constipation (24.9% versus 14.6%, $P = 0.002$), dyspnea (10.6% versus 5.7%, $P = 0.028$), fatigue (67.4% versus 51.3%, $P < 0.001$), infections (61.1% versus 52.9%, $P = 0.042$) and stomatitis (32.9% versus 7.6%, $P < 0.001$; Table 3). There was no difference in terms of serious AEs (8.0% versus 9.2%, $P = 0.667$) between treatment arms. Details on AEs by

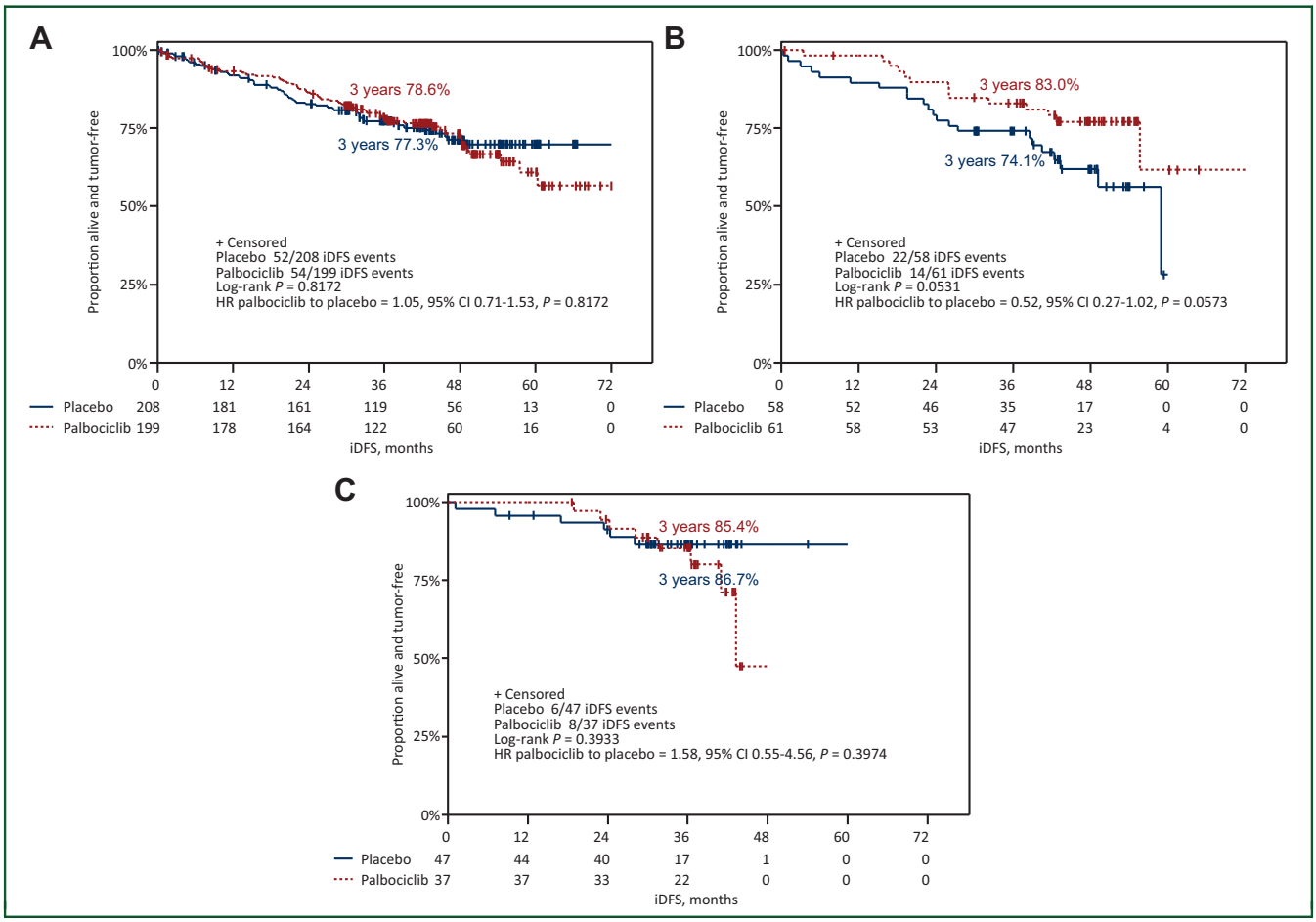

Figure 2. Kaplan–Meier curves for iDFS in premenopausal patients. iDFS by treatment arm in patients receiving (A) tamoxifen alone, (B) tamoxifen + GnRHa and (C) AI + GnRHa.

AI, aromatase inhibitor; CI, confidence interval; GnRHa, gonadotropin-releasing hormone analogue; HR, hazard ratio; iDFS, invasive disease-free survival.

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Table 3. AEs >10% (and SAEs <10%) in either treatment arm in premenopausal patients by treatment arm (all causality)

AE	Grade	Palbociclib *N* = 301 *n* (valid %)	Placebo *N* = 314 *n* (valid %)	Overall *N* = 615 *n* (valid %)	*P* value
Patients with AE	Any	300 (99.7)	313 (99.7)	613 (99.7)	1.00
Patients with grade 3/4 AE	3-4	244 (81.1)	58 (18.5)	302 (49.1)	<0.001
Patients with hematologic AE	Any	298 (99.0)	263 (83.8)	561 (91.2)	<0.001
Patients with hematologic grade 3/4 AE	3-4	229 (76.1)	6 (1.9)	235 (38.2)	<0.001
Patients with non-hematologic AE	Any	299 (99.3)	312 (99.4)	611 (99.3)	1.00
Patients with non-hematologic grade 3/4 AE	3-4	57 (18.9)	52 (16.6)	109 (17.7)	0.461
Patients with SAEs		24 (8.0)	29 (9.2)	53 (8.6)	0.667
Anemia	Any	230 (76.4)	105 (33.4)	335 (54.5)	<0.001
	3-4	1 (0.3)	1 (0.3)	2 (0.3)	1.000
Leukopenia	Any	298 (99.0)	232 (73.9)	530 (86.2)	<0.001
	3-4	173 (57.5)	3 (1.0)	176 (28.6)	<0.001
Neutropenia	Any	286 (95.0)	78 (24v8)	364 (59.2)	<0.001
	3-4	218 (72.4)	5 (1.6)	223 (36.3)	<0.001
Febrile neutropenia	Any	6 (2.0)	1 (0.3)	7 (1.1)	0.064
Thrombocytopenia	Any	185 (61.5)	59 (18.8)	244 (39.7)	<0.001
	3-4	2 (0.7)	0 (0.0)	2 (0.3)	0.239
Non-hematologic toxicities					
ALAT increased	Any	57 (18.9)	69 (22.0)	126 (20.5)	0.370
	3-4	1 (0.3)	1 (0.3)	2 (0.3)	1.000
Blood AP increased	Any	43 (14.3)	49 (15.6)	92 (15.0)	0.653
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
ASAT increased	Any	58 (19.3)	54 (17.2)	112 (18.2)	0.532
	3-4	2 (0.7)	1 (0.3)	3 (0.5)	0.617
Hyperkalemia	Any	26 (8.6)	37 (11.8)	63 (10.2)	0.232
	3-4	2 (0.7)	2 (0.6)	4 (0.7)	1.000
Hypernatremia	Any	33 (11.0)	28 (8.9)	61 (9.9)	0.420
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Hypocalcemia	Any	132 (43.9)	104 (33.1)	236 (38.4)	0.008
	3-4	3 (1.0)	0 (0.0)	3 (0.5)	0.117
Hypomagnesemia	Any	88 (29.2)	92 (29.3)	180 (29.3)	1.000
	3-4	2 (0.7)	0 (0.0)	2 (0.3)	0.239
Alopecia	Any	31 (10.3)	22 (7.0)	53 (8.6)	0.153
Arthralgia	Any	114 (37.9)	112 (35.7)	226 (36.7)	0.616
	3-4	2 (0.7)	2 (0.6)	4 (0.7)	1.000
Back pain	Any	34 (11.3)	39 (12.4)	73 (11.9)	0.709
	3-4	3 (1.0)	0 (0.0)	3 (0.5)	0.117
Bone pain	Any	47 (15.6)	52 (16.6)	99 (16.1)	0.826
	3-4	1 (0.3)	0 (0.0)	1 (0.2)	0.489
Blood creatinine increased	Any	32 (10.6)	25 (8.0)	57 (9.3)	0.269
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Constipation	Any	75 (24.9)	46 (14.6)	121 (19.7)	0.002
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Cough	Any	51 (16.9)	53 (16.9)	104 (16.9)	1.000
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Dyspnea	Any	32 (10.6)	18 (5.7)	50 (8.1)	0.028
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Diarrhea	Any	58 (19.3)	44 (14.0)	102 (16.6)	0.084
	3-4	1 (0.3)	1 (0.3)	2 (0.3)	1.000
Fatigue	Any	203 (67.4)	161 (51.3)	364 (59.2)	<0.001
	3-4	8 (2.7)	3 (1.0)	11 (1.8)	0.135
Headache	Any	73 (24.3)	87 (27.7)	160 (26.0)	0.358
	3-4	2 (0.7)	2 (0.6)	4 (0.7)	1.000
Hot flushes	Any	157 (52.2)	172 (54.8)	329 (53.5)	0.519
	3-4	3 (1.0)	4 (1.3)	7 (1.1)	1.000
Vulvovaginal dryness	Any	33 (11.0)	36 (11.5)	69 (11.2)	0.899
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Infection	Any	184 (61.1)	166 (52.9)	350 (56.9)	0.042
	3-4	7 (2.3)	15 (4.8)	22 (3.6)	0.129
Pyrexia	Any	38 (12.6)	27 (8.6)	65 (10.6)	0.116
	3-4	2 (0.7)	1 (0.3)	3 (0.5)	0.617
Insomnia	Any	47 (15.6)	57 (18.2)	104 (16.9)	0.452
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Myalgia	Any	63 (20.9)	50 (15.9)	113 (18.4)	0.119
	3-4	1 (0.3)	1 (0.3)	2 (0.3)	1.000
Nausea	Any	80 (26.6)	73 (23.2)	153 (24.9)	0.352
	3-4	0 (0.0)	1 (0.3)	1 (0.2)	1.000
Vomiting	Any	28 (9.3)	34 (10.8)	62 (10.1)	0.593
	3-4	0 (0.0)	2 (0.6)	2 (0.3)	0.499

Continued

Table 3. Continued

AE	Grade	Palbociclib $N = 301$ *n* (valid %)	Placebo $N = 314$ *n* (valid %)	Overall $N = 615$ *n* (valid %)	*P* value
Edema peripheral	Any	57 (18.9)	54 (17.2)	111 (18.0)	0.601
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Lymphedema	Any	34 (11.3)	30 (9.6)	64 (10.4)	0.511
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Pain in extremity	Any	36 (12.0)	31 (9.9)	67 (10.9)	0.439
	3-4	1 (0.3)	1 (0.3)	2 (0.3)	1.000
Muscle spams	Any	33 (11.0)	23 (7.3)	56 (9.1)	0.125
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	NA
Stomatitis	Any	99 (32.9)	24 (7.6)	123 (20.0)	<0.001
	3-4	2 (0.7)	1 (0.3)	3 (0.5)	0.617

AEs, adverse events; ALAT, alanine aminotransferase; AP, alkaline phosphatase; ASAT, aspartate aminotransferase; NA, not applicable; SAEs, serious adverse events.

treatment arm according to first ET are given in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103466.

Comparing AEs according to first ET, anemia G1-4 was significantly less frequent with AI + OFS (39.3%) compared to tamoxifen alone (56.7%) or tamoxifen + OFS (59.7%), as was thrombocytopenia G1-4 (23.8% versus 41.6% versus 45.4%), as these side-effects are caused by tamoxifen. The ATAC study, which compared the efficacy and safety of anastrozole and tamoxifen as adjuvant treatment for postmenopausal women with early-stage BC, also showed more frequent thrombocytopenia and anemia with tamoxifen than with the AI.[23] Arthralgia G1-4 was significantly more frequent in patients receiving an AI + OFS (69.0%) compared to tamoxifen alone (34.0%) or tamoxifen + OFS (22.7%), as were G1-4 hot flushes (71.4% versus 51.5% versus 47.1%), vulvovaginal dryness (20.2% versus 9.6% versus 10.9%) and fatigue (71.4% versus 59.6% versus 49.6%; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103466).

Palbociclib and ovarian function

Overall, 576 patients had serum samples available at baseline, 526 before C7 and 541 at EOT, respectively. At baseline, 58.7% of patients in the palbociclib arm and 58.4% of the patients in the placebo arm had postmenopausal E2 and FSH levels ($P = 1.000$). Of these, 80.4% remained postmenopausal at C7 and 77.2% at EOT with no significant differences between treatment arms (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.103466).

Of the patients with premenopausal E2/FSH levels at baseline, 9.1% under palbociclib versus 13.5% under placebo ($P = 0.387$) developed postmenopausal hormone levels at C7 and 17.6% versus 14.5% ($P = 0.587$) at EOT, respectively. Among patients aged <40 years, 28.1% in the palbociclib arm versus 24.7% in the control arm ($P = 0.728$) had postmenopausal hormone levels at baseline, 19.2 versus 12.5% at C7 ($P = 0.276$) and 27.4 versus 14.5% ($P = 0.054$) at EOT, respectively. The majority of patients not receiving OFS had postmenopausal hormone levels at baseline (80.3%) and remained postmenopausal throughout the study treatment (72.2% at C7 and 71.4% at EOT) without any significant differences between treatment arms at any time point. Although there was no overall difference in the fertility level of AMH, the group receiving palbociclib had slightly higher postmenopausal levels at the EOT.

Overall, the rate of non-fertile AMH levels at baseline was high (92.7%) and remained stable throughout the study (94.6% at EOT). No significant differences in the rate of non-fertile AMH levels were observed between treatment arms and subgroups at any time point (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.103466).

Especially in the subgroup of patients aged <40 years, the rate of non-fertile AMH levels was not significantly influenced by palbociclib.

DISCUSSION

In this exploratory subgroup analysis of the PENELOPE-B trial, the addition of palbociclib to standard ET did not improve iDFS in premenopausal patients at high risk of recurrence after NACT. These results are consistent with the previously published main overall results of the PENELOPE-B trial.[12]

The monarchE trial showed an improvement in iDFS with 2-year abemaciclib together with ET in the overall cohort and suggested a greater benefit in premenopausal patients.[15,16] Considering that younger age is correlated with higher risk of relapse, it seemed reasonable to explore survival within the premenopausal subgroup. However, our current analysis does not support an interaction between menopausal status and adjuvant palbociclib. One possible explanation might be that a longer or even more intensive CDK4/6i therapy is needed to elicit cytotoxic rather than cytostatic effects. PENELOPE-B had the shortest treatment duration but the longest FU of all the adjuvant CDK4/6i trials, although an FU of 42.8 months is defined as relatively short for an ER+/HER2− BC population. This hypothesis, however, does not explain the lack of benefit from 2 years of adjuvant palbociclib in the PALLAS study.[13] A subgroup analysis of PALLAS according to menopausal status has not been reported yet. However, benefit from the addition of palbociclib to ET was not seen in patients younger or older than 50 years, respectively. There are speculations whether the observed iDFS benefit in the monarchE trial was in part caused by informative censoring caused by the open-label

design.[24] In fact, the PENELOPE-B trial was the only placebo-controlled study compared to open-label design used in the PALLAS, monarchE and NATALEE trials. Moreover, the NATALEE trial is equipped with a comparably high power of 93% for the final analysis and interim analysis was reported at a very early phase since 79.2% of the patients had not yet completed the planned therapy.[25] This might be of major relevance for subsequent analyses. The publication of positive results in an open-label trial with the majority of patients still having to complete therapy will presumably lead to enhanced therapy adherence in the experimental arm and pronounced censoring in the control arm, which ultimately is able to influence the final survival analysis. However, the different observations in NATALEE, monarchE and PENELOPE-B trials might also be drug-specific.

The toxicity profile of palbociclib in premenopausal women was consistent with the intent-to-treat population, with a significantly higher rate of hematologic AEs but similar rate of non-hematologic AEs. However, some low-grade but relevant non-hematologic toxicities like fatigue and stomatitis were observed more frequently with palbociclib. As expected, the type of ET also impacted AEs, with the combination of an AI + OFS in PENELOPE-B leading to significantly higher rates of particularly bothersome side-effects compared to tamoxifen alone or tamoxifen + OFS, including arthralgias, bone pain, hot flushes and vulvovaginal dryness, irrespective of the treatment arm. The arthralgia rate in the PENELOPE-B trial was lower in patients treated with palbociclib (41.2%) compared to the placebo group (46.8%).[12] This trend can be confirmed in all CDK4/6i trials (PALLAS: 38.2% palbociclib + ET versus 45.0% ET and monarchE: 26.5% abemaciclib + ET versus 37.8% ET).[26,27] An exact cause for this is still unknown; however, based on the current data, a protective effect of CDK4/6i against joint inflammation and the occurrence of arthralgias can be assumed.[28] At the same time, patients treated with an AI + OFS had a numerically superior 3-years iDFS compared to patients receiving tamoxifen ± OFS. PENELOPE-B was not designed to investigate differences between ET in premenopausal women since the choice of the ET was not randomized and is subject to a selection bias, especially by age as described in the results. However, these data are in line with data from SOFT and TEXT studies.[1] In a high-risk population of premenopausal women, the additional benefit from AI + OFS over tamoxifen might justify higher rates of side-effects to some extent. The addition of palbociclib to tamoxifen + OFS in premenopausal women did not increase side-effects compared to AI + OFS and appeared highly effective. Further studies are needed in this case to evaluate the potential benefit of palbociclib in premenopausal patients receiving tamoxifen + OFS as a potential alternative to AI + OFS for better tolerability, especially in patients who cannot tolerate the side-effects of AI.

As there are no data on the effect of CDK4/6i on OF, a prospective evaluation of hormone levels was carried out in PENELOPE-B. As expected, after NACT most patients had postmenopausal hormone levels at randomization, even if defined as premenopausal by the investigator based on the menstrual and medical history. The addition of palbociclib to the ET after NACT did not significantly influence E2 and FSH levels in women who were reported premenopausal by investigators at study entry. More importantly, no effect was seen in patients with proven premenopausal hormone levels at baseline. Among patients not receiving OFS, the majority had postmenopausal hormone levels at baseline and remained postmenopausal throughout the study, without difference between treatment arms. We cannot make any conclusions as to a potential resumption of OF beyond the 12 months' treatment period, as no blood was collected beyond EOT. In PENELOPE-B, 50.3% of patients aged <40 years and 65.4% <35 years were already receiving OFS at baseline, rendering them functionally postmenopausal, although it is generally recommended to start OFS only in patients with proven OF. This led to interferences in the analysis of E2 and FSH levels. Consequently, this also led to the manageable proportion of premenopausal patients of 33% who received OFS.

Fertility preservation is an important issue in premenopausal patients undergoing treatment for early BC. As shown in prospective analyses, AMH levels are a surrogate of persistent ovarian dysfunction.[29-31] Our data demonstrate no significant impact of palbociclib on fertile AMH levels. However, the high rate of non-fertile AMH levels at baseline even in patients with premenopausal hormone levels or in patients aged <40 years is intriguing. This is in line with our previously published data on AMH levels in patients aged ≤45 years treated with (neo)adjuvant chemotherapy for early BC.[32] In PENELOPE-B, no additional impact of palbociclib on fertility as assessed via AMH levels was seen in patients with proven premenopausal hormone levels or <40 years of age at baseline. These results underline the importance of fertility-preserving measure before induction of chemotherapy whenever indicated.

As this analysis is based on a 1-year treatment period, we cannot firmly conclude that longer treatment with CDK4/6i as used in the other adjuvant trials may not have an impact on OF or on ovarian reserve.

In conclusion, in PENELOPE-B, the addition of 1-year of palbociclib to adjuvant ET did not improve iDFS in premenopausal patients. Ongoing trials will inform about the efficacy of a longer duration of adjuvant CDK4/6 inhibition in premenopausal patients. PENELOPE-B reports the first efficacy and safety results of palbociclib in combination with tamoxifen from a large adjuvant phase III trial and is the first analysis of adjuvant CDK4/6i therapy providing substantial information regarding fertility counseling. It is important to consider the high rate of non-fertile AMH levels in premenopausal patients after state-of-the-art NACT when counseling about fertility preservation and to take measures before start of chemotherapy.

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