Palbociclib combined with endocrine treatment in breast cancer patients with high relapse risk after neoadjuvant chemotherapy: Subgroup analyses of premenopausal patients in PENELOPE-B

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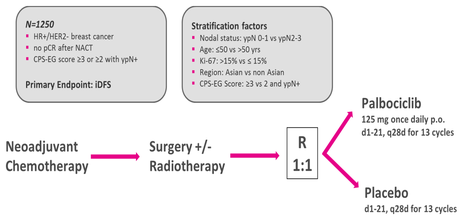
Background

PENELOPE-B assessed efficacy of the CDK4/6 inhibitor palbociclib for 1-year versus placebo added to endocrine therapy (ET) as post-neoadjuvant treatment in a high-risk breast cancer population. Palbociclib did not improve invasive disease-free survival (iDFS) compared to placebo (3-year iDFS 81.3% vs 77.7%)[1]. Here, we report results from the subpopulation of premenopausal women.

Patients and Methods

In PENELOPE-B (NCT01864746), patients with hormone receptor positive, HER2-negative breast cancer without pathological complete response after taxane-containing neoadjuvant chemotherapy and at high risk of relapse (CPS-EG score ≥3 or 2 and ypN+) were randomized to receive palbociclib or placebo in addition to standard endocrine treatment including tamoxifen +/- gonadotropin-releasing hormone analogue (GnRHa) or aromatase inhibitor (AI) +/- GnRHa (**Figure 1**). Menopausal status was assessed by the investigator. Survival curves were estimated using the Kaplan-Meier method and univariate Cox-proportional hazards models were used for iDFS to report hazard ratios with 95% CI. Fisher's exact test was used to compare frequencies of adverse events between arms and subgroups.

Figure 1 : PENELOPE-B Study Design



All patients will receive concomitantly endocrine therapy according to local standards

Results

Table 1: Baseline Characteristics of Premenopausal Patients

Parameter	Category	Palbociclib N=300 N (%)	Placebo N=316 N (%)
Age, years	<30	11 (3.7)	14 (4.4)
	30-<40	83 (27.7)	77 (24.4)
	40-<50	176 (58.7)	192 (60.8)
	50-<60	30 (10.0)	33 (10.4)
	median (range)	43 (22 - 55)	43 (19 - 56)
Tumor stage at surgery	ypT0 /ypTis	14 (4.6)	8 (2.5)
	ypT1/2	218 (72.7)	251 (79.7)
	ypT3/4	68 (22.7)	56 (17.8)
Histological nodal status at surgery	ypN0	13 (4.4)	16 (5.1)
	ypN+	284 (95.6)	297 (94.9)
Histological type	lobular	24 (8.0)	24 (7.6)
Grading	G3	71 (28.0)	92 (34.1)
Ki-67%, central pathology	>15%	71 (23.7)	71 (22.5)
CPS-EG score*	1	4 (1.3)	6 (1.9)
	2	118 (39.3)	130 (41.1)
	3	147 (49.0)	141 (44.6)
	4	27 (9.0)	32 (10.1)
	5	4 (1.3)	7 (2.2)

CPS-EG, clinical, pathological stage-estrogen receptor and grading; *based on non-missing total

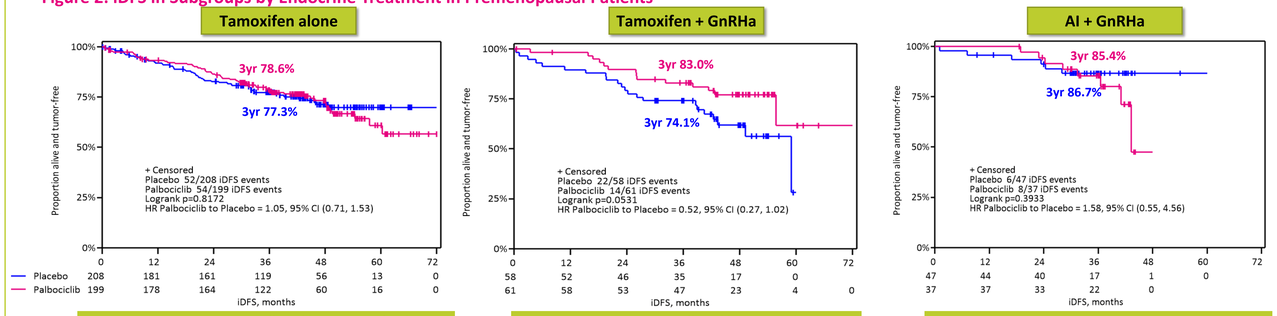
Table 2: Endocrine Therapy in Premenopausal Patients

Parameter	Palbociclib N=300 N (%)	Placebo N=316 N (%)	p-value
Start ET prior to Palbociclib/Placebo	272 (90.7)	286 (90.5)	1.000
Concomitant start of ET and Palbociclib/Placebo	28 (9.3)	30 (9.5)	
First ET applied			
Tamoxifen alone	199 (67.0)	208 (66.5)	0.593
Tamoxifen + GnRHa	61 (20.5)	58 (18.5)	
AI + GnRHa	37 (12.5)	47 (15.0)	
AI alone	3	3	

AI, aromatase inhibitor ; ET, endocrine therapy; GnRHa, gonadotropin-releasing hormone analogue; *Patients received AI alone were excluded from analyses according to first ET treatment

616/1250 patients randomized in Penelope-B were premenopausal at the time of enrollment, baseline characteristics are shown in **Table 1**. The majority of patients started with tamoxifen alone (**Table 2**). Overall, there was no difference in iDFS between palbociclib and placebo in premenopausal women (HR 0.95, 95% CI 0.69-1.30) with 3-year iDFS of 80.6% and 78.3%, respectively. Only in the small subgroup of patients treated with tamoxifen + GnRHa, there was a tendency for a better iDFS with palbociclib (interaction p=0.124) (**Figure 2**).

Figure 2: iDFS in Subgroups by Endocrine Treatment in Premenopausal Patients

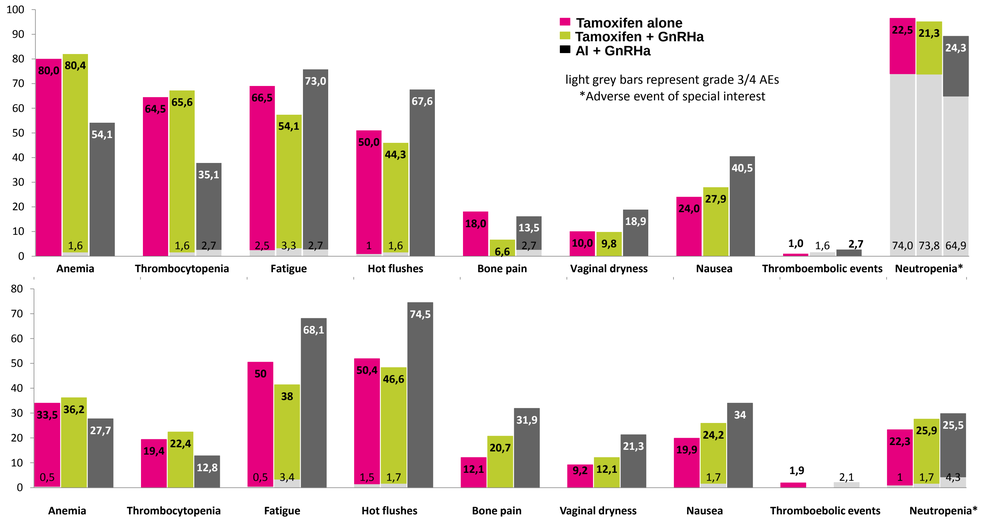


Event-free survival rate	Palbociclib (N=199)	Placebo (N=208)
Estimated 3-year iDFS rate % (95% CI)	78.6% (72.0%, 83.8%)	77.3% (70.8%, 82.6%)

Event-free survival rate	Palbociclib (N=61)	Placebo (N=58)
Estimated 3-year iDFS rate % (95% CI)	83.0% (70.8%, 90.5%)	74.1% (60.8%, 83.5%)

Event-free survival rate	Palbociclib (N=37)	Placebo (N=47)
Estimated 3-year iDFS rate % (95% CI)	85.4% (68.4%, 93.7%)	86.7% (72.8%, 93.8%)

Figure 3: Any Grade Adverse Events in Palbociclib and Placebo arm in Premenopausal Patients



Hematologic toxicity was significantly more common with palbociclib. Non-hematological toxicities any grade palbociclib vs placebo were: fatigue 67.4% vs 51.3%; hot flushes 52.2% vs 54.8%; bone pain 15.6% vs 16.6%; and vaginal dryness 11.0% vs 11.5%. Adverse events (any and high-grade) for palbociclib and placebo according to the endocrine treatment subgroups are shown in **Figure 3**.

Conclusions

1. **These are the first safety results from a phase III study for the combination tamoxifen +/-GnRHa and palbociclib.**
2. **Although the overall results did not show improvement in 3-year iDFS, an improvement was seen in the small subgroup of premenopausal women receiving tamoxifen + GnRHa. These results are mainly hypothesis generating and merit confirmation.**
3. **The addition of palbociclib to tamoxifen +/-GnRH in premenopausal women did not increase side effects compared to AI+GnRH and seems to be an alternative to AI+GnRHa.**

References

1. Loibl et al. J Clin Oncol 2021;

Presented at ASCO Annual Meeting 2021, Virtual Meeting, June 4-8.

The trial was financially supported by Pfizer, Inc.