Overall survival and updated invasive disease-free survival results from the Penelope-B trial investigating palbociclib vs placebo for patients with high-risk HR+/HER2- breast cancer and residual disease after NACT

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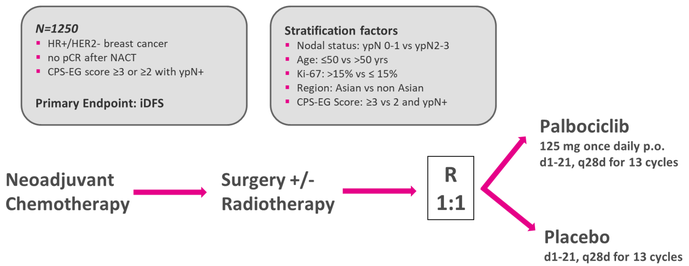
Background

- Risk of relapse for patients (pts) with hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC) after neoadjuvant chemotherapy (NACT) increases with higher CPS-EG scores despite adjuvant endocrine therapy (ET)[1].
- The PENELOPE-B trial tested adding palbociclib (palb) for one year to standard adjuvant ET in high-risk (CPS-EG score ≥3 or 2 with ypN+) HR+/HER2- BC pts, following its success in the advanced setting[2-5].
- After a median follow-up of 42.8 months, the final analysis for the primary endpoint invasive disease-free survival (iDFS) showed no improvement, nor did the interim analysis for overall survival (OS)[6].
- Final analysis for the secondary endpoints overall survival, updated analysis for iDFS, invasive breast cancer-free survival (iBCFS) and distant disease-free survival (DDFS) are presented.

Study design

PENELOPE-B (NCT01864746, GBG 78) was a phase III, multicenter, multinational, randomized, double-blind, placebo-controlled trial. Pts received either palb 125 mg or placebo (pb) on days 1-21 every 4 weeks for 13 cycles, alongside standard ET. Eligible pts (n=1250) were randomized 1:1 in permuted blocks (4/6), stratified by CPS-EG score, nodal involvement, Ki-67, age, and global region.

Figure 1: Study design



Statistical methods

All analyses were conducted on intention-to-treat (ITT) set. Survival probabilities were estimated using the Kaplan-Meier method with 2-sided 95% confidence intervals (CI) calculated via log-log transformation. The hazard ratio (HR) relative to placebo was determined using both univariate and multivariate Cox regression models. Similar analyses were done for other time-to-event endpoints. A two-sided stratified log-rank test (α error of 0.05) was used to compare treatment arms. No adjustments were made for multiple comparisons in the stratified subgroup analyses.

Results

- The baseline characteristics of the overall population are shown in **Table 1**. After a median follow-up of 77.8 months, we recorded 225 deaths [(108 palb; 117 placebo) HR 0.87, 95% CI 0.67-1.14, p=0.31] with a 6-year OS rate of 82.4% vs. 80.3% (**Figure 2, top panel**). No significant improvement was noted for palb versus placebo for iDFS (HR 0.94, 95% CI 0.78-1.14, p=0.55) and other time-to-event endpoints in the overall population (**Figure 2, top panel**).
- A higher nodal burden after NACT (ypN2-3: HR 1.37, 95% CI 1.04-1.81, p=0.025), larger tumor size post-NACT (ypT3/4: HR 1.40, 95% CI 1.03-1.9, p=0.034), CPS-EG Score ≥3 (HR 1.56, 95% CI 1.22-2.18, p=0.008), and baseline Ki67 >15% (HR 2.21, 95% CI 1.68-2.91, p<.001) were all found to be independent prognostic factors associated with poorer OS.
- However, in the post-hoc analysis of the invasive lobular BC subtype (n=110), those receiving palb (n=58) showed a notable trend towards better survival outcomes compared to those receiving placebo (n=52). The estimated 6-year rates for OS and iDFS were 88.8% and 73.5%, for the palb group, and 73.2% and 51.1% for the placebo group, respectively with a HR of 0.45 (95% CI 0.19-1.07, p=0.062) for OS and 0.52 (95% CI 0.28-0.97, p=0.035) for iDFS (**Figure 2, bottom panel, Figure 3**). Out of 22 observed deaths (n=8 palb vs. n=14 placebo), 21 were related to BC.

Table 1: Patient / tumor characteristics at baseline

Parameter	Category	Overall N (%)
Age, years	<=50	701 (56.1)
	>50	549 (43.9)
Menopausal status	premenopausal	616 (49.3)
	postmenopausal	634 (50.7)
Histological nodal status at surgery	ypN0-1	620 (49.6)
	ypN2-3	630 (50.4)
Ki-67	<=15%	931 (74.5)
	>15%	319 (25.5)
Risk status	CPS-EG Score 2 and ypN+	508 (40.6)
	CPS-EG Score ≥3	742 (59.4)
First ET applied	Tamoxifen +/- ovarian suppression	622 (49.8)
	AI +/- ovarian suppression	628 (50.2)
Histological tumor type	ductal or ductal-lobular invasive	1103 (88.2)
	lobular invasive carcinoma	110 (8.8)
	mucinous carcinoma	11 (0.9)
	invasive micropapillary carcinoma	5 (0.4)

Figure 2: Kaplan-Meier curves for survival

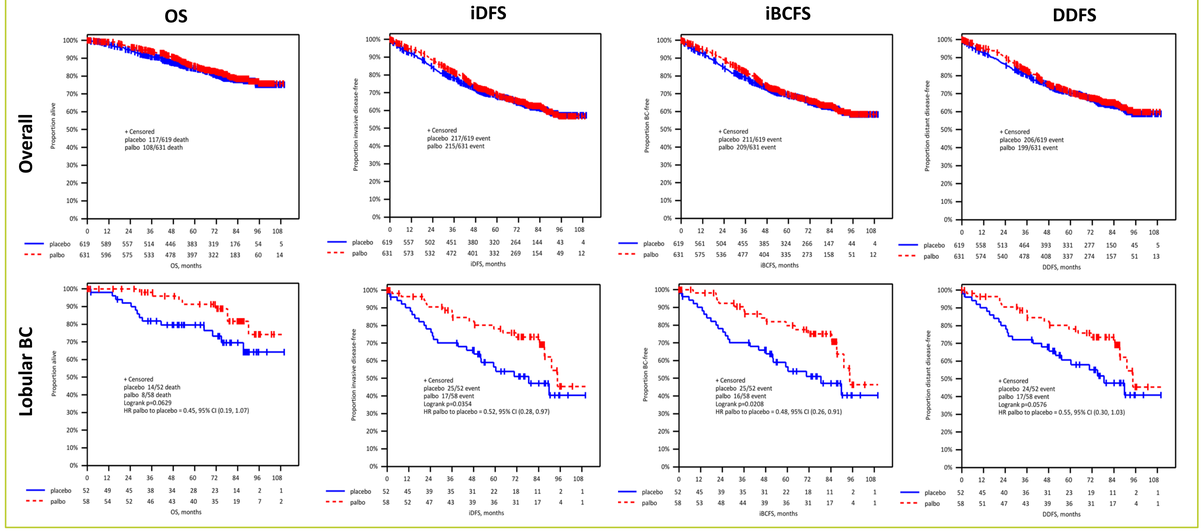
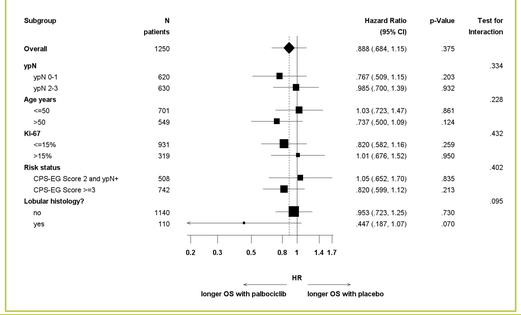


Figure 3: Forest plot of subgroup analyses for OS



Conclusion

The Penelope-B trial did not show a significant overall survival benefit from adding palbociclib in the overall population nor did it show improvements in the other survival endpoints with prolonged follow-up. Known prognostic factors for poorer OS were not associated with treatment efficacy. Exploratory analyses suggest that patients with lobular breast cancer may experience benefits. However, these results are limited by a small sample size and exploratory nature of the analysis. This highlights the need for further research into biomarkers for personalized treatment strategies.

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Presented at: ESMO-Congress-2024, 13 - 17 Sep 2024, in Barcelona, Spain.

This study was conducted as a collaboration between GBG and Pfizer. GBG is the study sponsor.
Pfizer funded the Penelope-B study and provided study drug.