Overall survival and disease recurrence rates in patients with invasive lobular breast cancer of the Penelope^{B} cohort

PO4-02-04

Hervé Bonnefoi[1], Frederik Marmé[2], Miguel Martin[3,4], Michael Untch[5], Sung-Bae Kim[6], Harry D. Bear[7], Nicole Mc Carthy[8], Karen Gelmon[9], José Angel García-Sáenz[10], Catherine M. Kelly[11], Toralf Reimer[12], Zhe Zhang[13], Masakazu Toi[14], Hope S. Rugo[15], Michael Gnant[16], Andreas Makris[17], Nader Hirmas[18], Valentina Nekljudova[18], Johannes Holtschmidt[18], Sibylle Loibl[18]

[1]Institut Bergonié and Université de Bordeaux INSERM U1312, Bordeaux, France; [2]Medical Faculty Mannheim, Heidelberg University, University Hospital Mannheim, Germany; [3]Instituto de Investigacion Sanitaria Gregorio Marañon, CIBERONC, Universidad Complutense, Madrid, Spain; [4]Spanish Breast Cancer Group, GEICAM, Madrid, Spain; [5]Helios Kliniken Berlin-Buch, Germany; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [7]Division of Surgical Oncology, Massey Comprehensive Cancer Center, Virginia Commonwealth University, VCU Health, Richmond, VA, USA; [8]Breast Cancer Trials Australia and New Zealand and University of Queensland; [9]BC Cancer, Vancouver, British Columbia, Canada; [10]Service de Oncología Médica, Hospital Clínico San Carlos, Madrid, Spain; [11]Mater Private Hospital, Dublin and Cancer Trials Ireland Breast Group, Ireland; [12]Department of Obstetrics and Gynecology, University of Rostock, Rostock, Germany; [13]Pfizer Inc. San Diego, USA; [14]Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [15]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA USA; [16]Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [17]Institute of Cancer Research, Mount Vernon Cancer Centre, Northwood, United Kingdom, [18]German Breast Group, Neu-Isenburg, Germany

Background

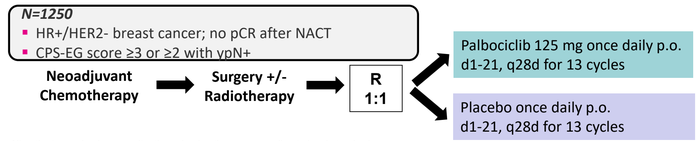
In the PENELOPE^{B} trial (GBG78; NCT01864746), the addition of 1-year of cyclin-dependent kinase 4/6 (CDK4/6) inhibitor palbociclib to standard endocrine therapy (ET) for women with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) early breast cancer at high risk of recurrence after neoadjuvant chemotherapy (NACT) did not improve invasive disease-free survival (iDFS) or overall survival (OS) in the main study analysis[1]. Invasive lobular breast cancer (ILC) accounts for ~15% of all breast cancers (BC) and represents an insufficiently investigated subtype of BC with typically less sensitivity to (neo)adjuvant chemotherapy, and poor distant disease-free survival (DDFS) irrespective of response to NACT[2,3,4]. Here, we report the post-hoc analysis results of iDFS, DDFS and OS in pre- and postmenopausal women with ILC enrolled in PENELOPE^{B}.

Patients and Methods

Patients with HR+/HER2-negative BC without pathological complete response (pCR) after taxane-containing NACT and at high risk of relapse (CPS-EG score ≥3, or 2 and ypN+) were randomized (1:1) to receive 13 cycles of palbociclib 125mg daily or placebo on days 1-21 of a 28-day cycle in addition to standard ET with tamoxifen (TAM) +/- gonadotropin-releasing hormone analogue (GnRHa) or aromatase inhibitor (AI) +/- GnRH (**Figure 1**). Randomization was stratified by nodal status at surgery, age at first diagnosis (≤50 vs. >50 years), Ki-67, region, and CPS-EG score. ILC diagnosis was locally assessed and reported by the investigators on the pathology case report form. The objectives of this post-hoc analysis were the evaluation of iDFS, DDFS and OS by treatment arm in patients with high risk ILC.

Statistical methods: The 3-year rates were assessed by the Kaplan-Meier product-limit method; stratified log-rank test and stratified Cox regression were used to compare both arms which are to be considered exploratory.

Figure 1: Trial Design



All patients received concomitantly endocrine therapy according to local standards

Results

A total of 1,250 patients were randomized, of whom 110 had ILC and were nearly uniformly distributed between both treatment arms (palbociclib n=58 vs. placebo n=52), with a slightly higher proportion of postmenopausal women (58.6% in the palbociclib arm vs. 53.8% in the placebo arm) compared to premenopausal women (41.4% in the palbociclib arm vs. 46.2% in placebo arm; **Table 1**). There was no difference in the distribution of AI/TAM use between the treatment arms. At the median follow up of 42 months, there was an estimated absolute but non-significant difference in 3-year-iDFS of 18.3% with palbociclib compared to placebo (iDFS 88.4% [95% CI 76.0-94.6] vs. 70.1% [95% CI 55.3-80.7]) with a hazard ratio (HR) of 0.66 [95% CI 0.27 – 1.61, log-rank p=0.354] was observed (**Figure 2**). A comparable 3-year-DDFS difference of 16.3% was observed (**Figure 3**). An estimated 3-year-OS difference of 16.4% (98.0% [95% CI 86.6 – 99.7] vs. 81.6% [95% CI 67.5 – 90.0]) with a HR of 0.27 (95% CI 0.05 – 1.43, log-rank p=0.108) was observed (**Figure 4**). Out of 12 observed deaths (n=2 palbociclib vs. n=10 placebo), all except one in placebo arm were related to metastatic BC.

Table 1: Baseline Characteristics

Parameter	Category	Palbociclib arm N=58 N(%)	Placebo arm N=52 N(%)
Age at first diagnosis	<= 50 yrs	29 (50.0%)	26 (50.0%)
	> 50 yrs	29 (50.0%)	26 (50.0%)
Menopausal status	Premenopausal	24 (41.4%)	24 (46.2%)
	postmenopausal	34 (58.6%)	28 (53.8%)
First ET	TAM +/- OS [2]	25 (43.1%)	22 (42.3%)
Histological tumor stage at surgery	ypT0	1 (1.7%)	1 (1.9%)
	ypT1	11 (19.0%)	8 (15.4%)
	ypT2	18 (31.0%)	19 (36.5%)
	ypT3	25 (43.1%)	23 (44.2%)
	ypT4	3 (5.2%)	1 (1.9%)
Histological nodal status at surgery	ypN0	2 (3.5%)	3 (5.9%)
	ypN1	23 (40.4%)	14 (27.5%)
	ypN2	21 (36.8%)	21 (41.2%)
	ypN3	11 (19.3%)	13 (25.5%)
CPS-EG score [1]	1	1 (1.7%)	0 (0.0%)
	2	30 (51.7%)	22 (42.3%)
	3	18 (31.0%)	23 (44.2%)
	4	9 (15.5%)	6 (11.5%)
	5	0 (0.0%)	1 (1.9%)
Ki-67%, local, core biopsy	<= 15%	15 (41.7%)	19 (51.4%)
	> 15%	21 (58.3%)	18 (48.6%)

[1] CPS-EG score based on clean baseline data; [2] ovarian suppression

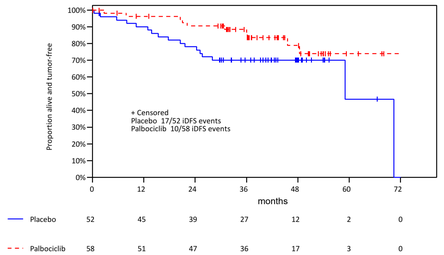


Figure 2: Invasive disease-free survival in two randomized treatment groups, Kaplan-Meier

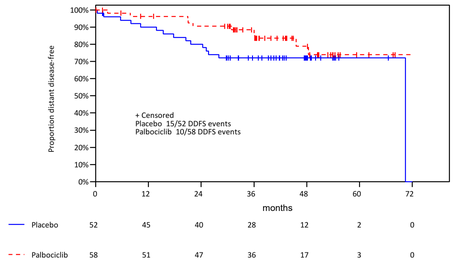


Figure 3: Distant disease-free survival in two randomized treatment groups, Kaplan-Meier

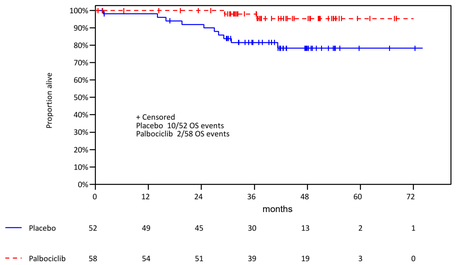


Figure 4: Overall survival in two randomized treatment groups, Kaplan-Meier

Table 2: Results of invasive disease-free survival, distant disease-free survival and overall survival.

		Palbociclib arm (n=58)	Placebo arm (n=52)
iDFS	No. of events	10	17
	3yrs iDFS	88.4% [95% CI 76.0-94.6]	70.1% [95% CI 55.3-80.7]
	HR [95%]	0.66 [0.27 – 1.61, log-rank p=0.354]	
DDFS	No. of events	10	15
	3yrs DDFS	88.4% [95% CI 76.0-94.6]	72.1% [95% CI 57.4-82.4]
	HR [95%]	0.84 [0.33 – 2.17, log-rank p=0.726]	
OS	No. of events	2	10
	3yrs OS	OS 98.0% [95% CI 86.6 – 99.7]	81.6% [95% CI 67.5 – 90.0]
	HR [95%]	0.27 [0.05 – 1.43, log-rank p=0.108]	

Conclusions

In this post-hoc analysis, a trend towards improvement in OS and a trend in favor of iDFS and DDFS for the addition of palbociclib to ET was observed among women with HR+/HER2- ILC at high risk of recurrence after NACT, but these differences were not statistically significant. This could represent a valuable treatment option for patients with high risk ILC. Due to the small sample size of the ILC subgroup, further follow-up evaluation is necessary. One limitation is that the allocation to the ILC subgroup was based on local assessment and not centrally confirmed. Moreover, analyses in the ILC subgroup from other adjuvant CDK4/6 inhibitor trials could substantiate these findings[5,6,7].

References

1. Loibl, S. et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-The Penelope-B Trial. J Clin Oncol 2021, 39:1518-30.
2. Desmedt, C. et al. Genomic Characterization of Primary Invasive Lobular Breast Cancer. J Clin Oncol. 2016, 34(16):1872-81.
3. Oesterreich, S. et al. Clinicopathological Features and Outcomes Comparing Patients With Invasive Ductal and Lobular Breast Cancer, JNCI 2022, 114(11):1511–22.
4. Van Baelen K, et al. Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer. Ann Oncol. 2022, 33(8):769-785.
5. Gnant M, et al. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2022, 40(3):282-293.
6. Johnston SRD, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023, 24(1):77-90.
7. Bardia, A. et al. LBA23 Invasive disease–free survival (iDFS) across key subgroups from the phase III NATALEE study of ribociclib (RIB) + a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+/HER2- early breast cancer (EBC). Ann Oncol. 2023, Volume 34, S1261 - S1262

Presented at: San Antonio Breast Cancer Symposium® - December 5-9, 2023

The trial was financially supported by Pfizer