Germline *BRCA*1/2 and other predisposition genes in high-risk early-stage HR+/HER2- breast cancer (BC) patients treated with endocrine therapy (ET) with or without palbociclib: A secondary analysis from the PENELOPE-B study

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Background

The PENELOPE-B trial (**Figure 1**) did not show an improved invasive disease-free survival (iDFS) by adding palbociclib to ET in high-risk HR+/HER2- BC.[1] In a HR+/HER2- patient population germline (g) *BRCA*1/2 mutations were observed in approximately 14% and *BRCA*1/2 plus other BC predisposition gene mutations in 20%.[2] In metastatic BC CDK4/6 inhibitors may have greater activity in patients with a *BRCA* mutation detected in ctDNA.[3] Here, we aimed to investigate the incidence of mutations in g*BRCA1/2* and other BC disposition genes (expected to be 10% and 13%, GBG data on file) and their impact on patient outcome in PENELOPE-B.

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+

Figure 1: PENELOPE-B study design

Neoadjuvant Chemotherapy → Surgery +/- Radiotherapy → R 1:1 → Palbociclib 125 mg once daily p.o. d1-21, q28d for 13 cycles / Placebo d1-21, q28d for 13 cycles

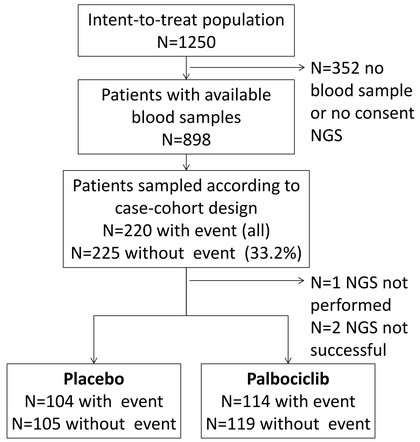
All patients endocrine therapy according to local standards

Patients and Methods

Blood samples from 898 of the 1250 PENELOPE-B patients were available. 445 patients were sampled following a case-cohort design[4] (all 220 cases defined as patients with any event during follow-up and 225 randomly selected patients without any event) and analyzed by targeted next generation sequencing (NGS) for germline variants in *BRCA1/2* and 16 non-*BRCA1/2* cancer predisposition genes: *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *FANCM*, *MRE11A*, *NBN*, *PALB2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11*, *TP53*, *XRCC2*.

The primary definition of mutational status was the prevalence of a pathogenic mutation (mt) in one or more analyzed BC predisposition genes. Statistical analyses were based on inverse probability weighting. For time-to-event endpoints (iDFS, distant disease-free survival [DDFS], and overall survival [OS]) weighted Cox proportional hazard models and weighted Kaplan-Meier estimates were used. Confidence intervals (CI) for 3-year survival rates and hazard ratios as well as interaction p-values were created by resampling.

Figure 2. Flow diagram



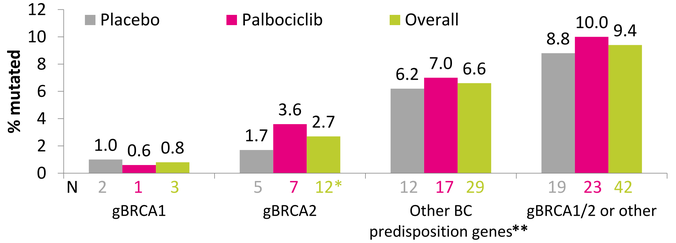
Results

Table 1. Baseline patient and tumor characteristics

Parameter	Category	Placebo N (%)*	Palbociclib N (%)*	Overall N (%)*
Age at diagnosis, years	≤50	120 (59.2)	133 (57.1)	253 (58.1)
	>50	89 (40.8)	100 (42.9)	189 (41.9)
Menopausal status	premenopausal	102 (50.1)	120 (51.0)	222 (50.6)
	postmenopausal	107 (49.9)	113 (49.0)	220 (49.4)
Global region	Non-Asian	195 (92.8)	215 (91.9)	410 (92.4)
	Asian	14 (7.2)	18 (8.1)	32 (7.6)
cT at first diagnosis	cT1/2	105 (52.4)	117 (52.4)	222 (52.4)
	cT3/4	103 (47.6)	116 (47.6)	219 (47.6)
cN at first diagnosis	negative	19 (9.3)	23 (11.3)	42 (10.3)
	positive	190 (90.7)	210 (88.7)	400 (89.7)
Ki67 % at randomization	≤15%	149 (77.6)	164 (76.0)	313 (76.8)
	>15%	60 (22.4)	69 (24.0)	129 (23.2)
Histological lymph node status at randomization	ypN 0-1	100 (49.2)	115 (49.5)	215 (49.3)
	ypN 2-3	109 (50.8)	118 (50.5)	227 (50.7)
Risk status at randomization	CPS-EG Score 2 and ypN+	77 (40.8)	88 (41.2)	165 (41.0)
	CPS-EG Score ≥3	132 (59.2)	145 (58.8)	277 (59.0)
ypT	ypT0/is/1/2	155 (75.8)	178 (79.0)	333 (77.5)
	ypT3/4	53 (24.2)	55 (21.0)	108 (22.5)
Grading	grade 1/2	119 (58.9)	139 (60.1)	258 (59.6)
	grade 3	86 (41.1)	91 (39.9)	177 (40.4)

***numbers given are unweighted, % are weigthed and do not consider missings (valid %);**

Figure 3: Mutations in g*BRCA* and other BC predisposition genes



Numbers given are unweighted, % are weigthed and do not consider missings (valid %); *one carried a g*ATM* mt and one a g*CHEK2* mt in addition to g*BRCA2* mt; **other BC predisposition genes were: n=8 CHEK2, n=7 PALB2, n=5 ATM, n=2 RAD50, n=1 for BARD1, FANCM, MRE11A, RAD51C, RAD51D, TP53 and n=1 for RAD51D and BRIP1

442 of 445 patients were successfully analyzed for mutational status (**Figure 2**). Baseline characteristics were well balanced between arms and are presented in **Table 1**. Mutations in g*BRCA* and other BC predisposition genes are summarized in **Figure 3**. The clinical baseline variables did not differ between patients with versus without mutation with respect to all genes analyzed. With regard to g*BRCA1* and g*BRCA2* genes only, age was different between patients with versus without mutation but not other clinical variables: All 15 (100%) g*BRCA*mt carriers were younger than 50 years compared to 238 (56%) wildtype (wt) patients.

After a median follow-up of 42.9 months, mutational status (mt vs. wt) based on all genes analyzed was not prognostic in terms of iDFS (**Figure 4**). Similar results were obtained for DDFS (hazard ratio 0.970, 95%CI 0.521-1.758) and OS (0.768, 95%CI 0.274-1.615). Neither mutated patients nor the wildtype patients had a benefit from palbociclib treatment (**Figure 5**); interaction tests for treatment arm/mutational status for all time-to-event endpoints were not statistically significant. Analysis by g*BRCA1/2* showed similar results but had less statistical power.

Figure 4. iDFS by mutation status (any mutation)

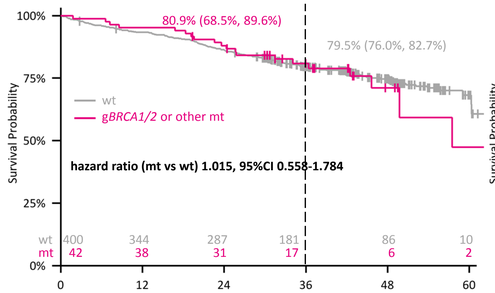
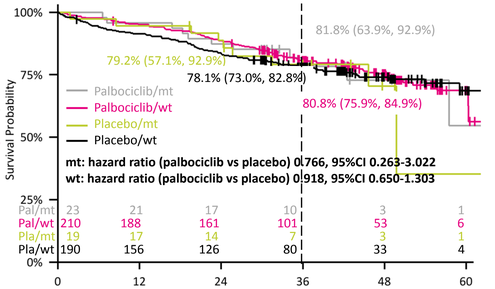


Figure 5. iDFS by treatment arm and mutation status



Numbers at risk given are unweighted, the Kaplan-Meier estimates and hazard ratios are weigthed

Conclusions

This case-cohort analysis of 442 patients enrolled in the PENELOPE-B trial is the largest investigation that analyzed BC predisposition genes in HR+ patients. The detection of BC predisposition genes was lower than expected.
In this subset of patients from the PENELOPE-B trial, patients with g*BRCA1/2* or other BC disposition genes had a comparable outcome to non-carriers overall and irrespective of treatment.

References

1. Loibl S, et al. J Clin Oncol 2021; 2. Pohl-Rescigno E, et al. JAMA Oncol 2020; 3. André F, et al. J Clin Oncol 2020; 4. Kulathinal S, et al. Epidemiol Perspect Innov 2007

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