Subgroup of post-neoadjuvant luminal-B tumors assessed by HTG in PENELOPE-B investigating palbociclib in high risk HER2-/HR+ breast cancer with residual disease

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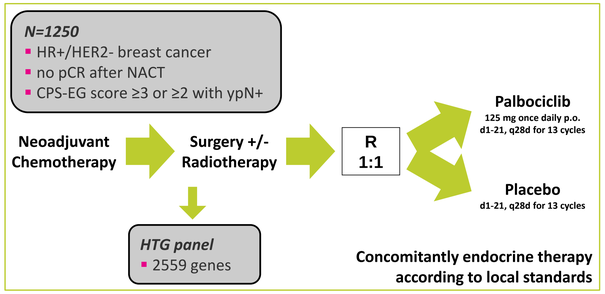
Background

About one third of patients with hormone-receptor-positive (HR+), HER2- primary breast cancer with residual invasive disease after neoadjuvant chemotherapy will relapse despite adjuvant endocrine therapy. Therapeutic inhibition of cyclin-dependent kinase 4 and 6 (CDK 4/6) by palbociclib combined with endocrine therapy demonstrated highly relevant efficacy in metastatic breast cancer. The phase III PENELOPE-B (NCT01864746) study did not show a significant benefit from palbociclib in women with centrally confirmed HR+, HER2- primary breast cancer without a pathological complete response after taxane-containing neoadjuvant chemotherapy and at high-risk of relapse (CPS-EG score ≥3 or 2 and ypN+) for the primary endpoint[1].

Patients and Methods

After completion of neoadjuvant chemotherapy (NACT) and locoregional therapy, PENELOPE-B patients were randomized (1:1) to receive 13 cycles (1 year) of palbociclib 125 mg daily or placebo on days 1-21 in a 28d cycle in addition to standard endocrine therapy. Analysis of the primary endpoint of invasive disease-free survival (iDFS) was planned after 290 events. Secondary objective included iDFS in luminal-B group by treatment. Gene expression in post-neoadjuvant surgical residual tumor tissue samples was profiled using the HTG EdgeSeq Oncology Biomarker Panel targeting 2559 genes associated with tumor biology (HTG Molecular Diagnostics Inc.). Based on 91 genes of this panel the Absolute Intrinsic Molecular Subtyping[2] (AIMS) was calculated.

Figure 1: Design of the PENELOPE-B study



Results

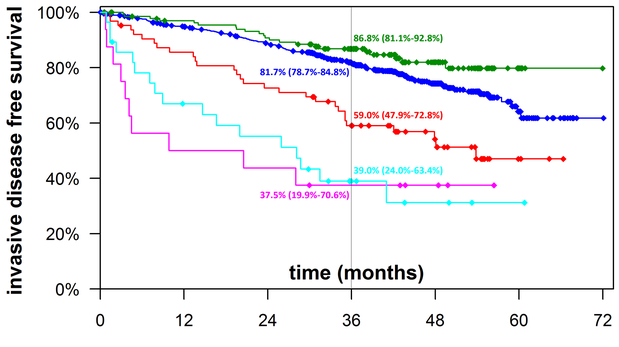
Table 1. Relation of clinical variables to AIMS subtype

Parameter	Category	LumA (n=663)	LumB (n=64)	p-value
		n (%)	n (%)	
Age (years)	≤50	365 (55.1%)	21 (32.8%)	**<0.001**
	>50	298 (44.9%)	43 (67.2%)	
Region of site	asia	41 (6.2%)	6 (9.4%)	0.291
	other	622 (93.8%)	58 (90.6%)	
cT	cT1-2	354 (53.5%)	36 (56.2%)	0.696
	cT3-4	308 (46.5%)	28 (43.8%)	
Grade	G1-2	439 (67.0%)	23 (35.9%)	**<0.001**
	G3	216 (33.0%)	41 (64.1%)	
Ki-67*	≤15%	516 (77.8%)	5 (7.8%)	**<0.001**
	>15%	147 (22.2%)	59 (92.2%)	
ypT	ypT0-2	516 (77.8%)	52 (81.2%)	0.635
	ypT3-4	147 (22.2%)	12 (18.8%)	
ypN	ypN0-1	306 (46.2%)	29 (45.3%)	1.000
	ypN2-3	357 (53.8%)	35 (54.7%)	
Risk status	CPS-EG=2, ypN+	289 (43.6%)	15 (23.4%)	**0.002**
	CPS-EG≥3	374 (56.4%)	49 (76.6%)	

*post-neoadjuvant IHC

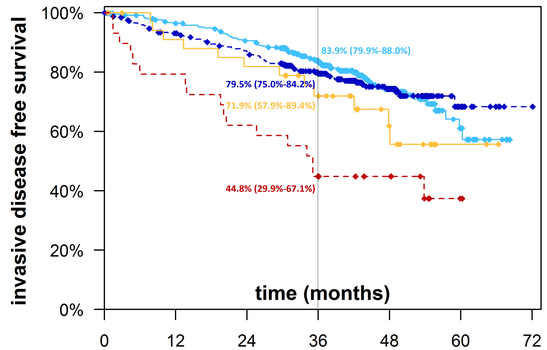
Gene expressions were measured in tumors after NACT from 906 of 1250 (72%) PENELOPE-B patients; 663 had LumA subtype, 64 LumB, 135 NormL, 16 BasalL, and 28 HER2E; for outcome see Figure 2. Compared to LumA the LumB patients were older, had higher post-neoadjuvant Ki-67, higher risk status (CPS-EG), and higher grade; no significant correlation was found for the region of participating sites, cT, ypT, and ypN (Table 1). Patients with LumB tumors had an estimated 3-year iDFS of 71.9% (Figure 3) with palbociclib vs 44.8% with placebo; the hazard ratio was 0.50 (0.24-1.05). Outcome was not different between treatment arms in patients with LumA tumors (3-year iDFS 83.9% vs 79.5%, hazard ratio 0.93 (0.68-1.28), interaction p=0.132); this was confirmed in multivariable analyses (Table2). Ki-67 by IHC and proliferation biomarkers from the HTG panel also showed no significant interaction with treatment.

Figure 2: iDFS by AIMS subtype (treatment arms combined)



LumA	663	604	555	405	176	32	1
LumB	64	53	45	33	19	3	0
NormL	135	125	117	93	45	6	0
BasalL	16	8	7	5	3	0	0
HER2E	28	17	14	6	3	1	0

Figure 3: iDFS by AIMS subtype and treatment in the AIMS-luminal cohort



palbociclib, LumA	340	316	292	217	94	19	0
placebo, LumA	323	288	263	188	82	13	1
palbociclib, LumB	35	30	27	21	10	2	0
placebo, LumB	29	23	18	12	9	1	0

Table 2. Cox models for biomarkers defining luminal-B subgroups

Model	n	AIMS LumA HR† (CI)	AIMS LumB HR† (CI)	Interaction p-value
AIMS-arm-interaction	727	0.93 (0.68-1.28)	0.50 (0.24-1.05)	0.132
multivariable*	718	0.91 (0.66-1.25)	0.45 (0.22-0.96)	0.097
Model	**n**	**MKI67 low HR† (CI)**	**MKI67 high HR† (CI)**	**Interaction p-value**
MKI67-arm-interaction	906	1.01 (0.68-1.51)	0.79 (0.56-1.11)	0.341
multivariable*	893	1.03 (0.69-1.54)	0.79 (0.56-1.12)	0.323
Model	**n**	**Ki-67 (IHC) ≤ 15 HR† (CI)**	**Ki-67 (IHC) > 15 HR† (CI)**	**Interaction p-value**
Ki-67-arm-interaction	1250	0.88 (0.66-1.17)	1.03 (0.72-1.46)	0.504
multivariable*	1229	0.87 (0.65-1.17)	1.00 (0.70-1.43)	0.568

†hazard ratios (HR) and confidence interval (CI) of iDFS for palbociclib vs placebo

*additional covariables: all variables listed in Table 1

Discussion

1. **PENELOPE-B did not show a statistically significant benefit from the addition of 1 year palbociclib to endocrine therapy compared to placebo plus endocrine therapy in the entire high-risk primary breast cancer study population.**
2. **However, the small group of patients with a luminal-B tumor after NACT (n=64) potentially derived benefit from palbociclib (numerically, not statistically significant).**
3. **Further investigation is required in a larger cohort to validate a palbociclib benefit that might be confined to this group.**
4. **It would be interesting to analyze biomarker differences between the post-NACT and the metastatic situation. It has been reported for the MONALEESA trials in metastatic breast cancer that most PAM50-based subtypes (with the exception of basal-like) did benefit from the addition of ribociclib to endocrine therapy[3]**

References

1. Loibl et al, JCO 2021
2. Paquet & Hallett, JNCI 2014
3. Prat et al, JCO 2021

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Collaborating study groups:

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