Immunohistochemical markers and determinants of clinical response in the Penelope-B trial

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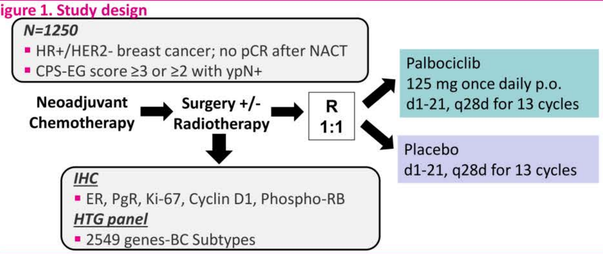
Background

The PENELOPE-B trial did not show improvement in invasive disease-free survival (iDFS) with the addition of palbociclib to endocrine therapy (ET) in patients with high-risk early breast cancer (BC) after neoadjuvant chemotherapy (NACT)[1]. Biomarkers may be able to identify subgroups of patients deriving benefit from palbociclib and guide future studies. Estrogen-receptor (ER), progesterone-receptor (PgR) and Ki-67 might be helpful in identifying patients benefiting from palbociclib. Furthermore, tumors with elevated expression of Cyclin D1 and phosphorylated retinoblastoma protein (phospho-RB) may harbor more dependency on CDK4/6 and thus higher sensitivity to palbociclib.

Figure 1. Study design



IHC Biomarkers, Subtypes, & Statistics

- Data for ER, PgR, Ki-67, HER2, Cyclin D1 and phospho-RB (Ser 807/811) immunohistochemistry were available from surgical resections after NACT from 1250 patients enrolled in PenelopeB.
- The percentage of positive ER and PgR cells and Ki-67 assessed in surgical specimens after NACT were combined to obtain the immunohistochemical score 3 (IHC3)[2]. Low vs high was based on the median IHC3 value.
- Cyclin D1 and phospho-RB Ser 807/811 immunoreactive (phospho-RB) scores were analysed in residual tumors after NACT (range 0-12 each).
- BC subtypes were determined using absolute intrinsic molecule subtyping-AIMS[3] on tumors for which HTG analyses had been performed on the biopsies (n=629) and residual tumors (n=782).

Proportional hazard regression model was used to assess the predictive and prognostic value of IHC3 and treatment on iDFS. Subgroup analysis was performed according to BC intrinsic subtypes (luminal-A/normal-like, luminal-B/HER2-enriched/basal) and HER2-status (HER2 0, HER2 low). Cox/Fine-Gray regression was used to define the predictive and prognostic value of CyclinD1 (≤1, >1), phospho-RB (≤2, >2) as dichotomized and continuous variables on iDFS, distant DFS (DDFS), locoregional invasive recurrence-free interval (LRRFI) and overall survival (OS). Multivariate analyses (MVA) were adjusted for age (≤50 vs >50), Ki-67 (≤15 vs >15), region (non-Asian vs Asian), ypN (ypN0-1 vs ypN2-3), risk status (CPS-EG=2 ypN+ vs ≥3), cT (cT1-2 vs cT3-4), ypT (ypT0-2 vs ypT3-4), and grade (G1-2 vs G3). The MVA for IHC3 include all the covariates above except Ki-67. p<0.05 was defined as statistically significant.

Results

Table 1. Baseline characteristics

Parameter	Value	Overall (%)
Age	<=50y	701 (56.1)
	>50y	549 (43.9)
Arm	Placebo	619 (49.5)
	Palbociclib	631 (50.5)
Her2 status	Her2-zero	598 (47.8)
	Her2-low	652 (52.2)
Ki-67	≤15	931 (74.5)
	>15	319 (25.5)
ER status	ER+	1236 (98.9)
	ER-	14 (1.1)
PgR status	PgR+	938 (75.0)
	PgR-	312 (25.0)

Parameter	Value	Overall (%)
T-stage (biopsy)	T1	89 (7.1)
	T2	583 (46.8)
	T3	373 (29.9)
	T4	201 (16.1)
Grade (biopsy)	G1/2	752 (60.9)
	G3	482 (39.1)
ypT	ypT0/2	986 (78.9)
	ypT3/4	263 (21.1)
ypN	ypN0/1	620 (49.6)
	ypN2/3	630 (50.4)

Overall, 98.9% of the patients had ER+ tumors, 75.0% PgR+, 52.2% had HER2 low, 25.5% Ki-67>15, median of the IHC3 score was high, 93.9% had Cyclin D1 >1, 57.8% had phospho-RB >2.

Table 2. Association of IHC3 with AIMS subtypes

Parameter	Value	ICH3 score (post-NACT) Low	ICH3 score (post-NACT) High	Overall	p-value
Pre-NACT AIMS	Basal	0 (0.0)	11 (3.5)	11 (1.8)	<.001
	HER2E	8 (2.5)	14 (4.5)	22 (3.5)	
	LumB	113 (35.5)	157 (50.5)	270 (42.9)	
	LumA	197 (62.0)	127 (40.8)	324 (51.5)	
	NormL	0 (0.0)	2 (0.6)	2 (0.3)	
	missing	305	316	621	
Post-NACT AIMS	Basal	1 (0.3)	14 (3.5)	15 (1.9)	<0.001
	HER2E	4 (1.0)	22 (5.5)	26 (3.3)	
	LumB	5 (1.3)	59 (14.8)	64 (8.2)	
	LumA	336 (88.0)	263 (65.8)	599 (76.6)	
	NormL	36 (9.4)	42 (10.5)	78 (10.0)	
	missing	241	227	468	

Figure 2. Prognostic significance of IHC3: **(A)** Patients with IHC3 score high had a worse iDFS compared to patients with IHC3 score low (MVA HR 2.29 95%CI [1.79-2.93], p<0.0001). **(B)** IHC3 was not predictive.

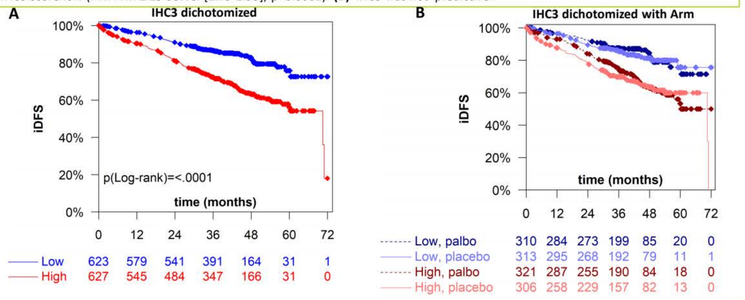


Figure 3. Predictive significance of IHC3 in luminal A/normal like tumors: **(A/B)** Patients with luminal-A/normal-like tumors (Pre-NACT AIMS) and IHC3 low had an improved iDFS with the addition of palbociclib to ET (MVA HR 0.35 95%CI (0.14-0.90), test for interaction p=0.01). **(C)** Patients with luminal-B/HER2/Basal tumors (Pre-NACT AIMS) IHC3 was not predictive.

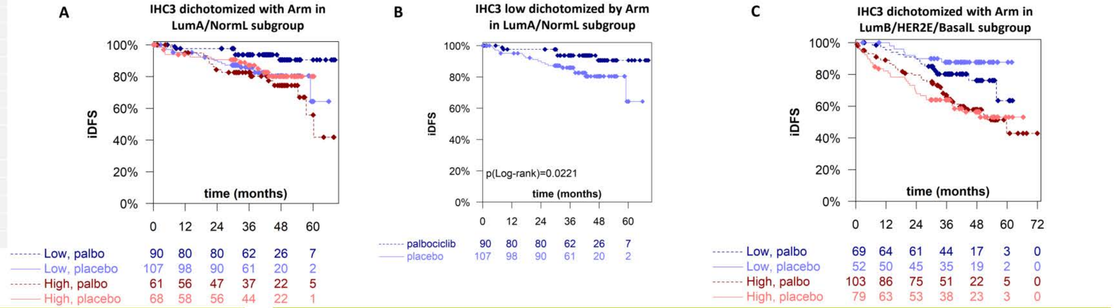


Figure 4. Prognostic significance of Cyclin D1: **(A)** Cyclin D1>1 is prognostic for iDFS (MVA HR 0.62 95%CI [0.41-0.94], p=0.023), LRRFI (MVA HR 0.30 95%CI (0.15-0.63), p=0.001) and OS (MVA HR 0.50 95%CI [0.28-0.89], p=0.019). Similar results when Cyclin D1 was analysed as continuous variable (not shown). **(B)** Cyclin D1>1 has no predictive value.

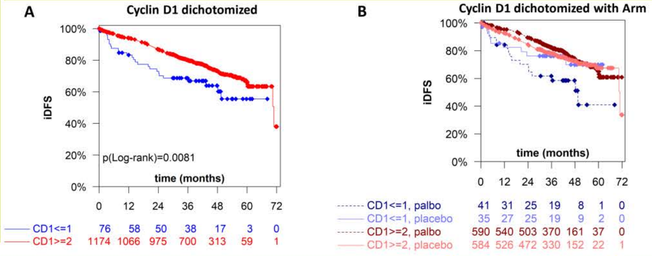
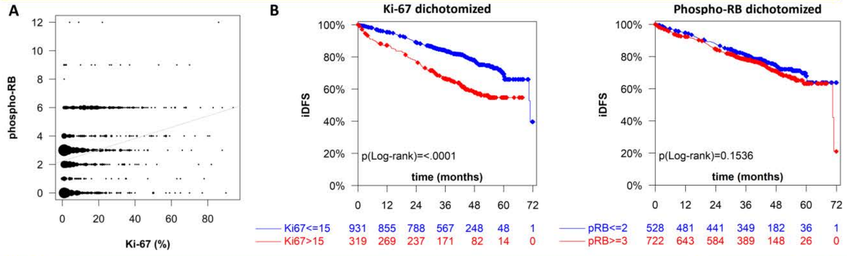


Figure 5. Role of phospho-RB and Ki67: **(A)** Bubble chart illustrating the correlation between Ki-67 and phospho-RB from resection samples (Spearman correlation coefficient 0.324, p<0.0001). The area of each bubble is proportional to the number of patients. The gray line denotes a linear regression model. **(B)** Ki-67, but not phospho-RB is prognostic at the cut-off points employed in PenelopeB.



Conclusions

- Patients with high Cyclin D1 tumor expression had a favorable prognosis independently from treatment arm.
- Phospho-RB is correlated with Ki-67, but in this analysis yields no additional prognostic or predictive information. High expression of Ki-67 was associated with poor prognosis.
- Patients with both, luminal-A/normal-like tumors and IHC3 low, had an improved outcome when receiving palbociclib in addition to adjuvant ET.
- Biomarkers can identify sub-groups of patients that experienced benefit with palbociclib in the PenelopeB study.

Future Directions

Validation of these findings in an independent cohort will be required to address the clinical benefit of the combination of palbociclib with ET in select patient sub-groups.

References

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