Outcome analysis of HER2-zero or HER2-low hormone receptor-positive (HR+) breast cancer patients - characterization of the molecular phenotype in combination with molecular subtyping

HER2-06

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Background

Breast cancer with low HER2 expression (HER2-low) is of high clinical relevance because of new therapeutic options with antibody-drug conjugates. We have recently shown in a large cohort from neoadjuvant clinical trials that HER2-low breast cancer has different molecular characteristics as well as different clinical outcomes compared to HER2-zero.[1] Considering the positive correlation between HER2-low expression and hormone receptor positivity observed consistently in many investigations, we have extended our analysis to HR+ tumors from the post-neoadjuvant PenelopeB trial[2]. In PenelopeB, patients with HR+ breast cancer (BC) and residual disease after neoadjuvant chemotherapy (NACT) were randomized to post-neoadjuvant palbociclib versus placebo in addition to endocrine therapy. We evaluated the molecular phenotype and clinical outcomes of HER2-low compared to HER2-zero patients.

Patients and Methods

A total of 1250 patients were randomized, HER2 status was available for 1152 tumors from pre-NACT core biopsies, determined by local pathology, and 1213 post-NACT tumors, determined as part of central pathology. For 1119 patients, a paired HER2-status was available. HER2-zero was defined as IHC0, and HER2-low was defined as IHC1+ or IHC2+/ISH-. Gene expression analysis of 2549 genes using the HTG oncology biomarker panel was performed in 629 pretherapeutic biopsies and 780 post-NACT residual tumor samples, with paired gene expression in 540 tumors. Breast cancer subtypes were determined using the AIMS approach.

Consort statement:

PenelopeB mITT cohort n=1250

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Core biopsies with (local) HER2 score n=1152 (n=629 with HTG mRNA data)

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Surgical resections with (central) HER2 score; n=1213 (n=780 with HTG mRNA data)

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Paired biopsies and surgical resections (n=1119) (n=540 with HTG mRNA data)

Table 1: Baseline data from pretherapeutic cohort

parameter	value	HER2-zero (n=457)	HER2-low (n=695)	Overall (n=1152)	P value
Age	≤50y	274 (60.0)	374 (53.8)	648 (56.3)	0.04
	>50y	183 (40.0)	321 (46.2)	504 (43.8)	
Region	Non-Asian	411 (89.9)	647 (93.1)	1058 (91.8)	0.06
	Asian	46 (10.1)	48 (6.9)	94 (8.2)	
Ki67	≤15	336 (73.5)	521 (75.0)	857 (74.4)	0.58
	>15	121 (26.5)	174 (25.0)	295 (25.6)	
Therapy arm	Placebo	226 (49.5)	346 (49.8)	572 (49.7)	0.91
	Palbociclib	231 (50.5)	349 (50.2)	580 (50.3)	
cT	cT1/2	250 (54.7)	380 (54.9)	630 (54.8)	0.95
	cT3/4	207 (45.3)	312 (45.1)	519 (45.2)	
	missing	0	3	3	
Tumor grade	G1-2	262 (58.2)	419 (61.1)	681 (59.9)	0.34
	G3	188 (41.8)	267 (38.9)	455 (40.1)	
	missing	7	9	16	
Histology	Ductal invasive	393 (87.3)	628 (91.7)	1021 (90.0)	0.03
	Lobular invasive	51 (11.3)	47 (6.9)	98 (8.6)	
	Others	6 (1.3)	10 (1.5)	16 (1.4)	
	missing	7	10	17	

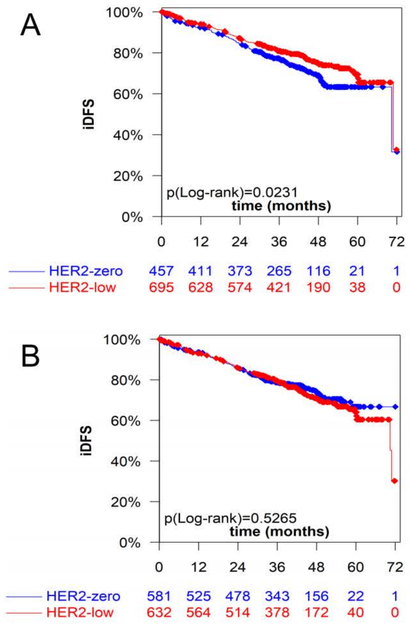

Figure 1: Prognostic impact of HER2-low status:
A: Improved prognosis of HER2-low tumors in pre-NACT biopsies (n=1152) **B:** No difference in prognosis in post-NACT samples (n=1213)

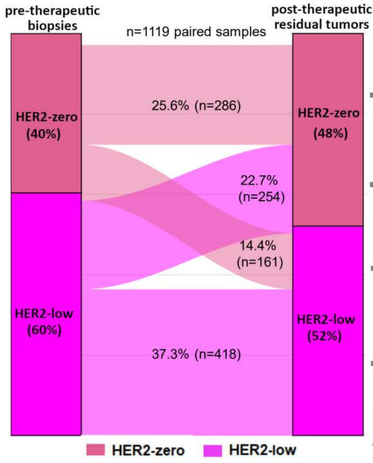

Figure 2: Changes in HER2-low status from core biopsy to residual tumor (n=1119)

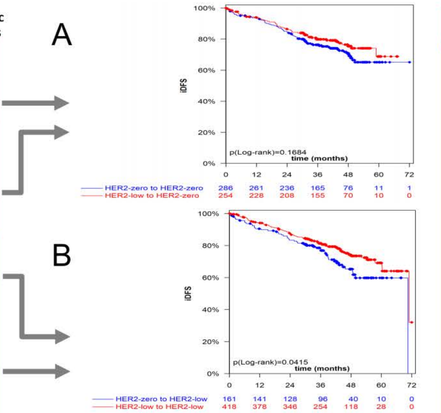

Figure 3: Survival analysis of alterations in HER2-low status:
A: No prognostic difference for tumors with new HER2-zero status after NACT (compared to persistently HER2-zero)
B: Reduced prognosis with new HER2-low status after NACT

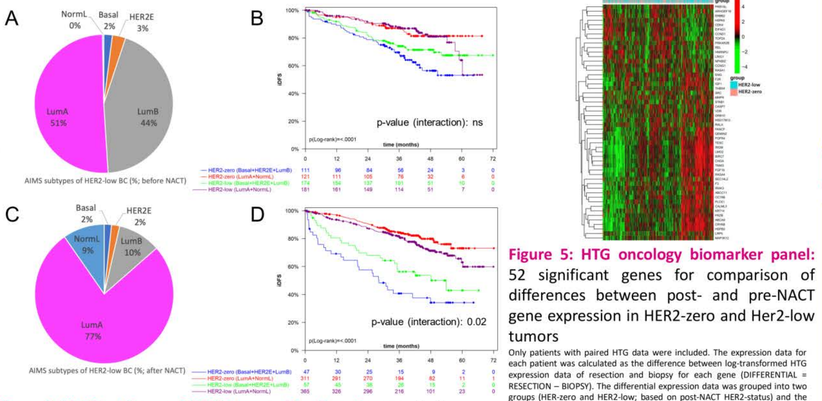

Figure 4: AIMS subtypes of HER2-low positive breast cancer before **(A,B)** and after **(C,D)** NACT: prevalence **(A,C)** and survival **(B, D)**

Figure 5: HTG oncology biomarker panel:
52 significant genes for comparison of differences between post- and pre-NACT gene expression in HER2-zero and Her2-low tumors

Only patients with paired HTG data were included. The expression data for each patient was calculated as the difference between log-transformed HTG expression data of resection and biopsy for each gene (DIFFERENTIAL = RESECTION – BIOPSY). The differential expression data was grouped into two groups (HER-zero and HER2-low; based on post-NACT HER2-status) and the Kolmogorov-Smirnov test was used to identify differences between both groups (p<0.05). 52 genes were identified, the hierarchical clustering of those genes did not result in a clear separation of HER2-low and HER2-zero tumors.

References

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Results

In pre-NACT biopsies, 695 tumors (60%) were HER2-low and 457 (40%) were HER2-zero. A HER2-low status pre-NACT was significantly linked to improved iDFS (HR 0.76 [95%CI 0.60-0.96], p=0.02, **Figure 1A**). In residual tumors, 632 tumors (60%) were HER2-low and 581 (40%) were HER2-zero, without any prognostic impact of HER2 low status (**Figure 1B**). A shift of HER2-status from core biopsy to residual tumor was observed in 415 (37%) of 1119 tumors (**Figure 2**). 161 (14%) had a shift from HER2-zero to HER2-low and 254 (23%) shifted from HER2-low to HER2-zero. A shift from HER2-low to HER2-zero was not associated with a significant survival difference (**Figure 3A**). In contrast, shifts from pre-NACT HER2-zero to post-NACT HER2-low were significantly linked to reduced iDFS (HR 1.43 [95%CI 1.01-2.01], p=0.04, **Figure 3B**), compared to the persistently HER2-low group. We did not observe a significant correlation of HER2-low status and AIMS subtypes. Only 3.1% of HER2-low tumors (pre-NACT) and 1.9% (post-NACT) had an HER2-enriched AIMS subtype; the majority were luminal A or B tumors (**Figure 4 A,C**). Significant iDFS differences were observed for HER2-low-status in combination with AIMS subtypes (lumB/basal/HER2E vs. lumA/normL; overall p-value <0.0001) for both pretherapeutic biopsies and residual tumor. Patients with post-NACT HER2-low tumors had an improved survival in aggressive AIMS subtypes (lumB/basal/HER2E), but not in the less aggressive AIMS subtypes (lumA/normL), with a positive test for interaction (p=0.02, **Figure 4D**). For the pre-NACT samples a similar, but non-significant trend was observed (**Figure 4B**). We used the HTG oncology biomarker panel to identify differentially expressed genes pre- and post-NACT. A total of 52 genes were significantly correlated with post-NACT HER2 status (**Figure 5**). Further evaluations are necessary to analyze the alterations of gene expression in the different HER2-low groups.

Conclusions

1. This is the first evaluation of neoadjuvant treated HER2-low patients in a prospective clinical trial cohort of high-risk HR+ BC. In this cohort, a HER2-low status in pre-NACT biopsies is related to improved disease-free survival.
2. A shift in HER2-low status was observed during chemotherapy, indicating an adaptation of pathway activity to therapy-induced stress, which might become relevant for future diagnostic and therapeutic approaches. In particular, a shift from HER2-zero to HER2-low was significantly linked to reduced survival.
3. A combination of AIMS subtypes and HER2-low status was relevant for prognosis, in particular in post-NACT samples.

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