Clinico-pathological and genomic features of HER2-low early Breast Cancer (eBC). Results of retrospective analysis of seven adjuvant trials by the Hellenic Cooperative Oncology Group (HeCOG)

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Hellenic Cooperative Oncology Group (HeCOG)

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Introduction

HER2-low breast cancers are a mixture of luminal and triple negative tumors. Precise molecular characterization could help refine treatment strategies with novel antibody-drug conjugates and improve outcomes in this patient subgroup.

Methods and Materials

Between **1996–2021**, **5,320 patients** with operable breast cancer were enrolled across **3 randomized** and **4 observational** studies, all receiving **dose-dense sequential chemotherapy** (taxanes and anthracyclines). **Adjuvant hormonal** and **radiation therapy** were given as indicated.

Tumor samples were analyzed mainly on **tissue microarrays (TMAs)**. Central **ER/PgR (HR)** and **HER2/ERBB2 IHC/FISH** were used to define subtypes:
HER2-low: IHC 1+ or 2+/FISH non-amplified, **HER2-zero:** IHC 0 and **Luminal A / Luminal B / TNBC**

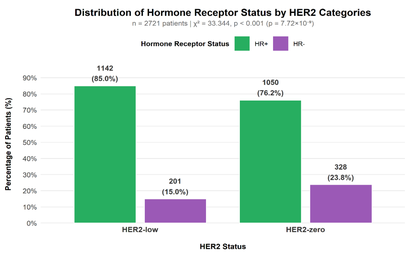
Retrospective analyses included **2,751 cases** with clinicopathologic and IHC data and **1,120 tumors** with **DNA NGS** results.
HER2 heterogeneity was assessed by comparing:
HER2-low_c: all cores consistently HER2-low (>0)
HER2-low_d: ≥1 core scored 0

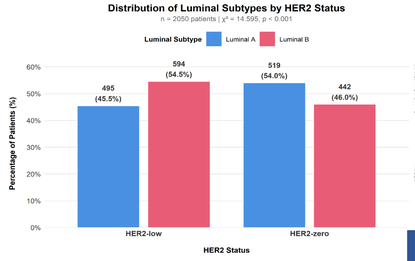
Patient Characteristics

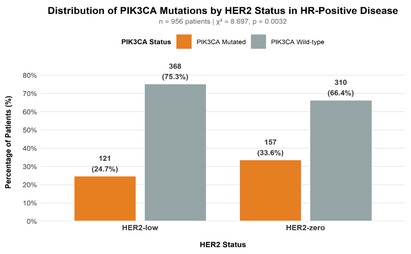
	Total study cohort	HR+	
Characteristics	2,751	2,192	
		HER2-zero	HER2-low
		1,050 (48)	1,142 (52)
Age (N=)	Median (range)		
	53 (21-83)	53 (24-79)	53 (22-83)
	N (%)	N (%)	N (%)
Menopausal status			
Premenopausal	1,231 (45)	476 (45)	513 (45)
Postmenopausal	1,520 (55)	574 (55)	629 (55)
Surgery			
Modified radical mastectomy	1,532 (56)	629 (60)	648 (57)
Simple mastectomy	4 (0.1)	2 (0.2)	1 (0.1)
Partial mastectomy	1,215 (44)	419 (40)	493 (43)
Tumor size			
≤ 2 cm	1,052 (38)	407 (39)	433 (38)
2.1-5 cm	1,455 (53)	542 (52)	613 (54)
>5 cm	243 (9)	101 (9)	95 (8)
Nodal status			
0	626 (23)	196 (19)	212 (18)
1 - 3	1,131 (41)	452 (43)	499 (44)
≥4	993 (36)	402 (38)	431 (38)
Histological grade			
1	182 (7)	87 (8)	84 (7)
2	1,253 (45.5)	563 (54)	575 (50)
3	1,307 (47.5)	398 (38)	481 (43)
Histological type			
Invasive (NST)	2,203 (80)	769 (73)	959 (84)
Invasive lobular	301 (11)	184 (18)	90 (8)
Other	247 (9)	97 (9)	93 (8)
Adjuvant Chemotherapy	2,748 (99)	1,050 (100)	1,139 (98)
Adjuvant HT	2,120 (77)	931 (89)	1,025 (90)
Tamoxifen	1,230 (58)	792 (85)	639 (62)
LH-RH	685 (32)	311 (33)	322 (31)
Aromatase inhibitor	1,091 (51)	500 (54)	518 (50.5)
Fulvestrant	9 (0.4)	3 (0.3)	5 (0.5)
Combined HT			
TAM followed by AI	294 (14)	99 (11)	173 (17)
LH-RH agonist with TAM	625 (29)	285 (31)	301 (29)
LH-RH agonist with AI	133 (6.3)	55 (6)	72 (7)
Adjuvant RT	2,028 (74)	776 (74)	821 (72)

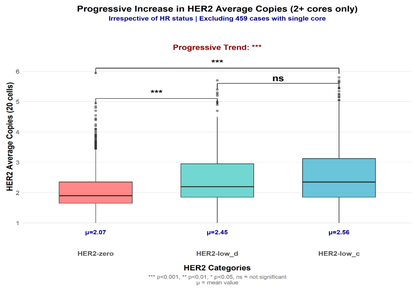
Results

- HER2-low tumors were more often HR + (p< 0.001)
- Within HR + disease only, the proportion of Luminal B was higher in HER2-low (51%) than HER2-zero (41.6%), whereas Luminal A showed the opposite pattern (p< 0.001)
- PIK3CA mutations on the other hand were more common in HER2-zero (33.6% vs. 24.7%, p=0.0036)
- A statistically significant progressive increase in ERBB2 average copies was observed from HER2-zero to HER2-low_d and HER2-low_c irrespective of HR status (p<0.001), with the primary distinction being between the HER2-zero and HER2-low_d categories
- IHC-based molecular subtypes (but not the HER2 subgroups) were prognostic of DFS and OS



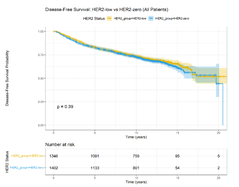




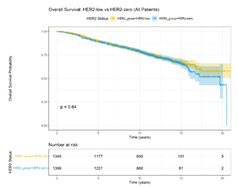


Survival

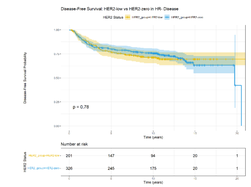
DFS



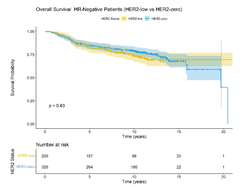
OS

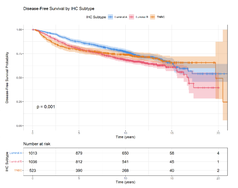


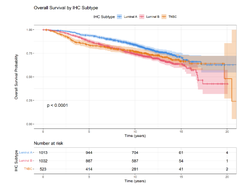
DFS

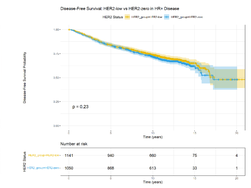


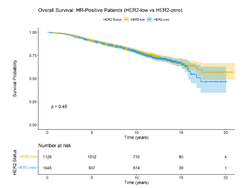
OS











Conclusions

Biological differences:
- HR+/HER2-low and HER2-zero early breast cancers (eBC) differ in estrogen receptor pathway activity.

Genomic profile:
- Higher frequency of PIK3CA mutations in HER2-zero vs. HER2-low HR+ tumors likely reflects Luminal A enrichment, consistent with the known association between Luminal A subtype and PIK3CA mutations.

HER2 quantitation:
- HER2 IHC levels correlate with underlying ERBB2 copy number.

Prognostic significance:
- IHC-based subtypes remain prognostically informative.
- Clinical HER2 thresholds do not appear to influence prognosis in this cohort.

Future directions:
- More **quantitative and reproducible** HER2 assessment methods may be needed to define subgroups relevant for **prognostication** and **therapeutic targeting**.

Contact

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