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Landscape of homologous recombination repair-related gene mutation and homologous recombination deficiency in Chinese patients with HER2-low early breast cancer

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Background

- HER2-low (IHC 1+ or IHC 2+/FISH-negative) early breast cancer (EBC) constitutes a significant proportion of breast malignancies[1].
- HRR-related gene mutation leading to HRD increases risks for tumorigenesis and has been proved as a viable therapeutic target in ovarian cancer and triple-negative breast cancer, with therapies such as PARP inhibitors and carboplatin[2,3].
- However, current evidence is largely derived from studies in European and American populations. Therefore, clinical research focusing on Chinese patients with HER2-low EBC is warranted.

Methods

- This prospective, single-center, observational study aimed to enroll 255 treatment-naïve patients with operable primary HER2-low invasive EBC, who had completed HRR-related gene mutation and HRD assessments.
- The HRD score was derived from the combined assessment of three genomic scar signatures: loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. HRD positivity was defined as an HRD score ≥42 and/or the presence of a *BRCA1/2* mutation. The primary outcome was to characterize the landscape of HRR-related gene mutations and HRD.

Results

- From August 2022 to September 2025, 129 of 255 planned patients were enrolled. The median age of the patients was 43 years (range 27-68). Tumors were predominantly stage I-II (108 [84%]); 103 (80%) were hormone receptor (HR)-positive (estrogen receptor ≥10%), and 102 (79%) had Ki67 expression ≥20% (**Table 1**). The median HRD score was 20 (Interquartile range 10-35), and 26 (20%) patients were HRD-positive (including 14 had g*BRCA1/2* mutation). HRD-positive status was more common in tumors with histological grade-III, HR-negative, or Ki67 expression ≥20%.

Table 1. Baseline characteristics

	All (n=129)	HRD positive (n=26)	HRD negative (n=103)	P value
Age, years				0.22
≤40	51 (40%)	13 (50%)	38 (37%)	
>40	78 (61%)	13 (50%)	65 (63%)	
Histological grade				0.01
I/II	87 (67%)	12 (46%)	75 (73%)	
III	42 (33%)	14 (54%)	28 (27%)	
TNM stage				0.15
I/II	108 (84%)	24 (92%)	84 (82%)	
III	21 (16%)	2 (8%)	19 (18%)	
HR status				<0.001
Positive	103 (80%)	14 (54%)	89 (86%)	
Negative	26 (20%)	12 (46%)	14 (14%)	
Ki67 expression				0.06
<20%	27 (21%)	2 (8%)	25 (24%)	
≥20%	102 (79%)	24 (92%)	78 (76%)	

- Among HRR-related gene mutations, *BRIP1* (17 [13%]), *NBN* (11 [9%]), *RAD51C* (11 [9%]), *PALB2* (8 [6%]), *BRCA 2* (8 [6%]), and *BRCA 1* (6 [5%]) were most common (**Figure 1**).
- Alterations were frequently observed in *PIK3CA* (58 [45%]), *TP53* (48 [37%]), *GATA3* (34 [26%]), *MYC* (22 [17%]), *CCND1* (21 [16%]), and *FGF3/4/19* (20 [16%]; **Figure 2**).

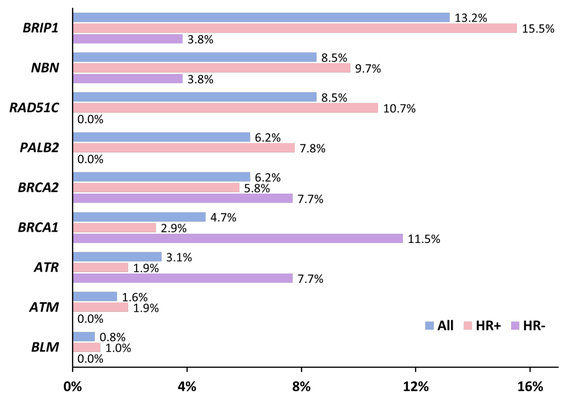


Figure 1. Frequency of HRR-related gene mutations



Figure 2. Landscape of top 30 cancer-related gene mutations

Conclusion

- This study delineates the landscape of HRR-related gene mutation and HRD in Chinese patients with HER2-low EBC. HRD-positivity was associated with histological grade III, HR-negative status, and Ki67 expression ≥20%. Further enrollment is warranted.

Ref.

1. Tarantino P, et al. ***JCO*** 2020, 38(17):1951-1962.
2. Robson M, et al. ***NEJM*** 2017, 377(6):523-533
3. Loibl S, et al. ***Lancet Oncol*** 2018, 19(4):497-509.

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