2021 ESMO congress

Clinical Implication of Gene Alterations Revealed by Comprehensive Genomic Profiling and Clonal Hematopoiesis in Breast Cancer Patients

298P

Lanxin Zhang, Lingzhi Xu, Chen Song, Na Li, Siwen Sun, Shanshan Zhao, Gena Huang, Man Li*

Department of Oncology, The Second Hospital of Dalian Medical University, Dalian Medical University, Dalian, China.

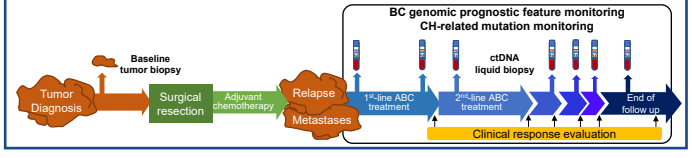
BACKGROUND

- Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer death in women. Around 30% of BC patients suffer from relapse and/or metastases after definitive treatment[1,2].
- Clonal hematopoiesis (CH), the abnormal expansion of clonally derived hematopoietic stem cells harboring leukemia related somatic mutations, increases the risk of therapy-related myeloid neoplasms and affects cancer development[3].
- Here, we identified prognostic genomic features of advanced breast cancer (ABC) patients at baseline, monitored their evolutionary patterns during ABC treatment, and explored the influence of CH-related mutations on prognosis.

METHODS

- A total of 101 BC patients with relapse and/or metastases were studied retrospectively.
- Comprehensive genomic profiling was performed using a broad next-generation sequencing (NGS) panel targeting 425 cancer-related genes.
- The clonal evolution and CH-realted mutations were tracked by collecting serial plasma samples and conducting circulating tumor DNA (ctDNA) tests (Figure 1).

Figure 1. ctDNA monitoring for clonal evolution and CH-related mutations.



RESULTS

Clinical Characteristics at Initial Diagnosis

- The median age at diagnosis of the entire study cohort was 46 years, and 56 (55%) patients were classified as HR+/HER2-. After relapse and/or metastases, 65 (64%) patients experienced at least 4 lines of ABC treatment (Table 1).

Table 1. Overview of patient clinical characteristics.

Characteristic	Total (n=101)	Baseline (n=35)	ctDNA monitoring (n=59)	*p*-value[a]
Age at initial diagnosis, No. (%)				0.54
< 50 y	57 (56.44)	16 (45.71)	32 (54.24)	
≥ 50 y	44 (43.56)	19 (54.29)	27 (45.76)	
Age at initial diagnosis, median (range), y	46 (28-82)	51 (30-68)	48 (28-74)	
Clinical stage at initial diagnosis, No. (%)				0.84
I	12 (11.88)	4 (11.43)	5 (8.47)	
II	31 (30.69)	8 (22.86)	22 (37.29)	
III	47 (46.53)	21 (60.00)	27 (45.76)	
IV	9 (8.91)	2 (5.71)	5 (8.47)	
Unknown	2 (1.98)	0 (0.00)	0 (0.00)	
Subtype at initial diagnosis, No. (%)				0.85
HR+/HER2-	56 (55.45)	18 (51.43)	31 (52.54)	
HR+/HER2+	9 (8.91)	2 (5.71)	6 (10.17)	
HR- /HER2+	15 (14.85)	5 (14.29)	12 (20.34)	
triple-negative breast cancer (TNBC)	21 (20.79)	10 (28.57)	10 (16.95)	
Initial therapy, No. (%)				0.95
Surgical resection	92 (91.09)	31 (88.57)	53 (89.83)	
Chemotherapy/Radiotherapy	3 (2.97)	2 (5.71)	2 (3.39)	
Targeted	5 (4.95)	2 (5.71)	4 (6.78)	
Immune	1 (0.99)	0 (0.00)	0 (0.00)	
Lines of treatment for ABC, median (range)	5 (1-12)	4 (1-11)	5 (1-12)	

Baseline Prognostic Genetic Features

- Thirty-five patients with formalin-fixed paraffin-embedded (FFPE) baseline tumour tissue samples were grouped as the "Baseline Cohort".
- The most frequently altered genes were *TP53* (51%), *PIK3CA* (31%), *MCL1* (26%), and *ERBB2* (20%) (Figure 2).
- *TP53* alternations were enriched in HR- patients ($p<0.01$).
- *TP53* mutations (95% CI 1.90-31.18), *CTCF/GNAS* mutations (95% CI 20.17-3204.48) and *NOTCH2* alterations (95% CI 1.08-63.39) were negatively associated with DFS (Figure 3-DFS), controlling for clinical characteristics.
- *TP53* (95% CI 1.01-71.38) and *NOTCH1* mutations (95% CI 1.69-84.36) were negatively associated with OS (Figure 3-OS), controlling for clinical characteristics.

Figure 2. Genetic profile of the Baseline Cohort.

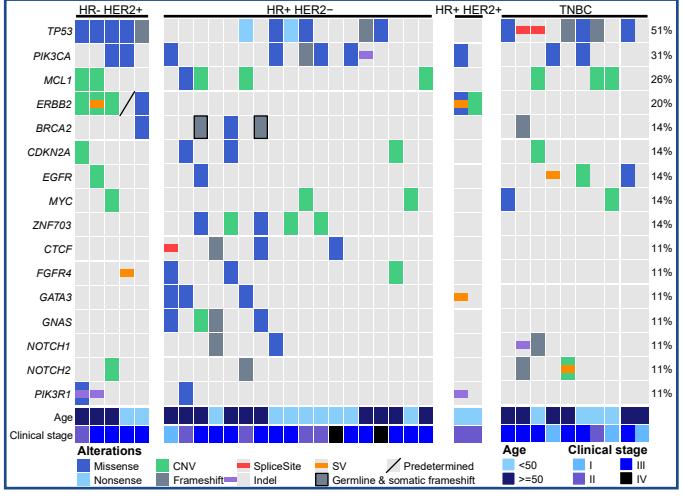
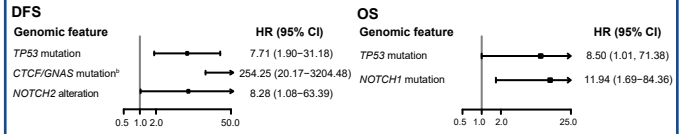


Figure 3. Baseline prognostic genomic features and adjusted hazard ratios (HRs).

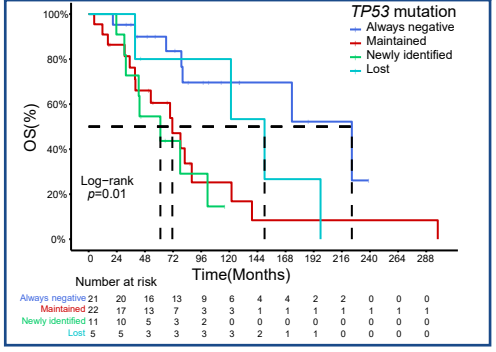


[a]Adjusted for age at diagnosis, clinical stage, BC subtype at initial diagnosis, neoadjuvant therapy and adjuvant chemotherapy.
[b]Co-mutation was observed in the *CTCF* and *GNAS* gene among 31 patients who received surgical resection as initial therapy in the Baseline Cohort.

Prognostic Value of *TP53* Mutation Evolutionary Pattern and CH

- Fifty-nine patients with serial plasma samples were grouped as the "ctDNA Monitoring Cohort", including 24 patients in the Baseline Cohort.
- The evolutionary pattern of *TP53* mutation was associated with the OS of ABC patients ($p=0.01$, Figure 4; Newly identified *vs.* Always negative, $p<0.01$).
- CH-related genetic mutations were identified in 6 patients and *DNMT3A* (83%) was the most frequently-observed gene.
- Statistically significant assoication was not found between CH-related mutations and the OS of ABC patients.

Figure 4. ABC prognosis in relation to newly identified *TP53* mutations.



SUMMARY

- The prognosis of ABC patients was negatively associated with baseline somatic genetic alterations of *TP53*, *CTCF*, *GNAS*, *NOTCH1*, and *NOTCH2*.
- The evolutionary pattern of *TP53* mutations in plasma samples after relapse and/or metastases could serve as a prognostic factor of poor prognosis for ABC patients.

REFERENCES
1. Winters, S., Martin, C., Murphy, D. and Shokar, N.K., 2017. Breast cancer epidemiology, prevention, and screening. Progress in molecular biology and translational science, 151, pp.1-32.
2. Palesh, O., Kamen, C., Sharp, S., Golden, A., Neri, E., Spiegel, D. and Koopman, C., 2018. Physical activity and survival in women with advanced breast cancer. Cancer nursing, 41(4), p.E31.
3. Park, S.J. and Bejar, R., 2020. Clonal hematopoiesis in cancer. Experimental hematology, 83, pp.105-112.

DISCLOSURE
The authors report no conflicts of interest.

CONTACT
Lanxin Zhang, MD, Department of Oncology, The Second Hospital of Dalian Medical University, Dalian Medical University
Email: 870907869@qq.com
Man Li, MD, Department of Oncology, The Second Hospital of Dalian Medical University, Dalian Medical University
Email: dmuliman@163.com