Inter-tumor heterogeneity in breast cancers: the dynamic evolution of cancer genome during the metastatic process

C. Fumagalli [1], A. Ranghiero [1], S. Gandini [2], F. Corso [2], S. Taormina [1], E. De Camilli [1], G. Viale [1,3], M. Barberis [1], E. Guerini Rocco [1,3]

[1]Division of Pathology and [2]Department of Experimental Oncology, IEO, European Institute of Oncology, IRCCS, Milan, Italy, [3]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

Background

Breast cancer genome evolves during malignant progression leading to spatial and temporal genomic heterogeneity. Here we performed comprehensive genomic profiling of primary breast cancers and matched recurrences focusing on shared and private alterations to identify potentially actionable genomic aberrations.

Methods

128 patients with primary breast cancers (n=72 Luminal B, n=56 Triple-negative) and at least one relapse within 17 years were included in this study. DNA and RNA from 289 tumor samples (primary and relapses) were subjected to Next-Generation Sequencing using comprehensive panels (FoundationeOne or Oncomine Comprehensive Cancer Assay v.3). Analysis was successfully performed for 188 samples, including 61 cases with matched primary tumor and relapse.

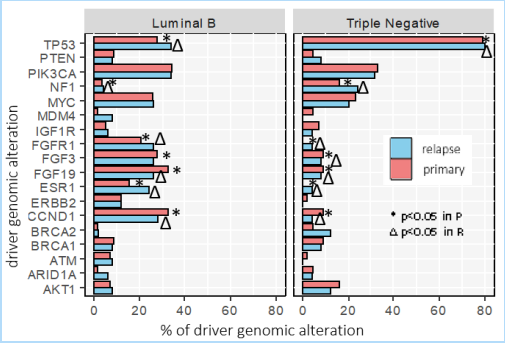

Figure 1: Genomic aberrations of primary tumors and relapses, according to molecular subtype.

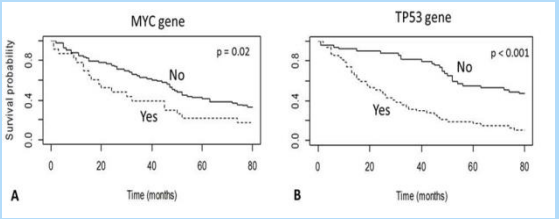

Figure 2: Kaplan-Meier (Log-rank test) analysis of disease-free survival according to the presence of (A) *MYC* amplification and (B) *TP53* mutation in primary tumors.

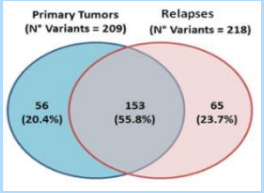

Figure 3: Venn diagram of shared and private driver alterations between primary tumors and matched relapses.

Gene	N° alterations associated to OncoKB level	OncoKB level
BRCA2	1	Level 2
CDKN2A	1	Level 4
ERBB2	1	Level 1
ESR1	6	Level 3A
FGFR1	2	Level 3B
MDM2	1	Level 3B
NF1	3	Level 4
PIK3CA	5	Level 1

Table 1: Actionable private alterations identified in the recurrences according to the OncoKB level.

Results

- In 10 of 128 (7.8%) cases molecular subtype (immunohistochemical surrogates) change was observed between primary tumor and matched relapse.
- The most frequent genomic alterations identified in both primary tumors and relapses were *TP53* (Primary=49%, Relapse=49%) and *PIK3CA* (Primary =33%, Relapse =30%) mutations, and *MYC* copy number gain (Primary=25%, Relapse=23%) (**Figure 1**).
- *TP53* and *NF1* alterations were more frequently identified in triple-negative tumors; *ESR1* mutations and *CCND1, FGF3, FGF19, FGFR1* copy number gains in tumors of luminal subtype (p<0.05) (**Figure 1**).
- In primary breast cancers, the number of alterations (p=0.06), the presence of *TP53* mutations (p<0.05) and *MYC* copy number gain (p<0.05) were associated with a shorter time to relapse (**Figure 2**).
- 55.8% of driver genomic aberrations were shared between primary tumors and matched relapses **(Figure 3)**.
- In 27 of 61 (44.3%) cases, additional driver alterations were identified in the recurrence only, including 20 genomic aberrations classified as level 1 – level 4 according to the OncoKB ranking **(Table 1)**.

Conclusions

Comprehensive genomic profiling of primary tumors identified genomic aberrations associated with time to relapse. A core of driver alterations was shared between primary tumor and matched relapse samples but actionable private alterations were detected in the recurrence.

Abstract ID 18P
Presenting Author *Caterina Fumagalli*
Email: *caterina.fumagalli@ieo.it*

This study was funded by ERA-NET TRANSCAN-2 programme in translational cancer research, EU framework programme Horizon 2020 of European Commission.