BACKGROUND

Metastatic breast cancer (MPBC) is a rare disease characterized by aggressive features and dismal prognosis after standard therapy. Herein, we report the molecular screening of the Milan National Cancer Institute case series for the evaluation of potentially druggable alterations.

METHODS

A total of 49 MPBC cases treated with curative intent were identified. Primary tumors were profiled using Oncomine Comprehensive Assay Plus panel (Thermo Fisher Scientific) for copy number alteration (CNA), tumor mutational analyses and burden (TMB) and microsatellite instability (MSI) analyses, according to the manufacturer instructions.

STUDY POPULATION

Herein, we report the results for the first 34 pathological reviewed cases. Among them, 94 unique genes harbored at least one mutation representing 24% of the panel. The median number of mutations indexed per patients was 4 (range 0-29). CDG1 (38%), TP53 (22%) and CDKN2A (19%). Twenty-five (25/34, 73%) cases showed actionable mutated genes, including PIK3, mTOR, FGFR3, FGFR4 were the most commonly mutated genes.

RESULTS

- 11 out of 17 altered genes were included within druggable categories with different extend as reported below.

**Druggable categories**

- Most of the cases showed low TMB, the median value being 4.5 (range 0-28). MSI status was high only in 2 cases. 2 cases (6%) showed high TMB status while 22 (64%) and 10 (34%) cases were characterized by low and intermediate status respectively.
- MSI status was detected as high and stable in 2 and 31 cases respectively. Only 1 samples was not evaluable for MSI (QC fail).

**Microsatellite instability status (MSI)**

- In the Hippo and RTK-RAS pathways the two types of alterations were instead equally represented whereas the remaining pathways (β-catenin/WWT, TGFβ, PI3K, NOTCH, NYCT and Cell cycle) were more affected by CNA than mutations. NR2 and TP53 signaling pathways were instead activated by mutational events only.

**Microsatellite instability status for each case. Red and blue color refer to MSI-High and MSI-Low respectively. Black dot refers to QC of MSI analysis**

- Common CNAs included 3q (10%), 5q (9%) and 17p (6%), with the top 3 altered genes represented by ERAP2 (7%), NDC1 and PARP4 (50%). Only DDR2 and RIT3 genes showed amplification (14%).

**Comparison between 10 canonical cancer pathway ( Vega F.S. et al., Cell 2018) enriched by mutational and/or CNA events. Fraction of pathway affected (A) and fraction of samples affected by mutational and/or CNA events were reported in brown and green respectively. “Fraction of pathway” and “fraction of samples” affected refer to the number of altered genes present in a specific pathway and to the number of cases showing the altered pathway, respectively.**

CONCLUSIONS

Mutational and copy number alterations conveyed complementary information in MPBC cooperating in activation of cancer pathways. These findings suggest to further study the value of CNAs in MPBC biological processes, especially immunogenicity, which cannot be explained by the low TMB and MSI found.

**DISCLOSURES**

None

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