Molecular profiling comparison of BRCA1/2-mutated and BRCA1/2 non-mutated triple-negative breast cancer (TNBC)

David Arguiello, MD; Brian Abbott, MD; Zoran Gatalica, MD/ScP; Sandee Reddy, MD; Elias Obeid, MD; Lori Goldstein, MD*
*Caris Life Sciences, Phoenix, AZ; Fox Chase Cancer Center, PA

Abstract

Background: Triple-negative breast cancer (TNBC) is a type of breast cancer that remains challenging because of ineffective targeted therapy and lack of effective targeted therapy for it. Molecular profiling has revealed different subtypes, indicating a potential for promising targeted therapy such as androgen blockade and PARP inhibition in some TNBCs. The purpose of this study is to identify differences in BRCA1/2-mutated and non-mutated TNBC to shed light on potential therapeutic options in both subtypes, utilizing a multiparameter approach.

Methods: A cohort of 386 triple-negative breast cancer specimens were tested via a multiparameter profiling service (Caris Life Sciences, Phoenix, AZ) consisting of gene sequencing (next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC] and FISH) and gene amplification (fluorescence or chromogenic in situ hybridization [FISH or CISH]). Primary and metastatic specimens were evaluated. Tumors with any BRCA1 and/or BRCA2 mutation (i.e., pathogenic or variant of unknown significance) were categorized as “BRCA1/2-mutated”, while all others were considered “BRCA1/2 non-mutated”.

Results: In our cohort, 16.3% (63/386) of specimens were BRCA1/2-mutated while 83.7% (323/386) had no BRCA2 alteration detected. Amongst the highest rates of protein expression in BRCA1/2-mutated and non-mutated specimens were biomarkers like TOP2A (63.5% and 63.4%), EGFR (65.2% and 67.4%), and the immune checkpoint L1CAM biomarker, PO-L1 (51.1% and 51.9%), with non-statistically significant differences. Differences noted between BRCA1/2-mutated and non-mutated specimens were detected by IHC in AR (11.1% versus 22.0%, p = 0.0309) and PTEN (47.6% versus 59.6%, p = 0.0041), with both trends reaching statistical significance. The overall highest mutation rate in both BRCA1/2-mutated and non-mutated were TP53 (80.6% and 73.1%, p = 0.2659). Differences were also noted between BRCA1/2-mutated and non-mutated specimens by NGS in APC (6.3% versus 1.9%, p = 0.0644) and PIK3CA (47.6% versus 59.6%, p = 0.0041), with both trends reaching statistical significance. The overall highest mutation rate in both BRCA1/2-mutated and non-mutated were TP53 (80.6% and 73.1%, p = 0.2659). Differences were also noted between BRCA1/2-mutated and non-mutated specimens by NGS in APC (6.3% versus 1.9%, p = 0.0644) and PIK3CA (47.6% versus 59.6%, p = 0.0041), with both trends reaching statistical significance.

Conclusion: Multiparameter tumor profiling identified differences in molecular profiles between BRCA1/2-mutated and BRCA1/2 non-mutated TNBC. Our findings raise the possibility for future investigation of potential combination specific targeted therapy and possibly improve treatment options.

Results (continued)

Figure 1 – Demographics. All TNBC specimens (n = 386) analyzed were female, with a median age of 56 years (standard deviation ± 11.8). In the BRCA1/2-mutated cohort, 44.4% (26/59) were under 50.

Figure 2 – Histologies represented in the cohort. The majority of specimens profiled were classified as either invasive ductal carcinomas (IDC) or unspecified breast carcinomas. Of note, one of the two squamous cell carcinomas (SCC) squamous specimens analyzed contained a BRCA1 mutation.

Table 1: Staining of BRCA1 and BRCA2 in TNBC. Of note, PD-L1 expression was lower in BRCA1/2-mutated (47.6% versus 59.6%, p = 0.0585). PTEN also showed a trend toward lower expression in BRCA1/2-mutated (47.6% versus 59.6%, p = 0.0585). PD-L1 expression was lower in BRCA1/2-mutated (47.6% versus 59.6%, p = 0.0585). PTEN also showed a trend toward lower expression in BRCA1/2-mutated (47.6% versus 59.6%, p = 0.0585). PD-L1 expression was lower in BRCA1/2-mutated (47.6% versus 59.6%, p = 0.0585). PTEN also showed a trend toward lower expression in BRCA1/2-mutated (47.6% versus 59.6%, p = 0.0585). PD-L1 expression was lower in BRCA1/2-mutated (47.6% versus 59.6%, p = 0.0585). PTEN also showed a trend toward lower expression in BRCA1/2-mutated (47.6% versus 59.6%, p = 0.0585).

Results (continued)

Figure 3 – Immunohistochemistry (IHC) in BRCA1/2-mutated and non-mutated samples. Comparisons were made between various potentially theranostic IHC evaluating protein expression. For some biomarkers, expression rates between BRCA1/2-mutated and non-mutated specimens were similar or not statistically significant, as evidenced by EGFR (65.2% and 67.4%), TOP2A (63.5% and 63.4%), and PO-L1 (51.1% and 51.9%), with both trends reaching statistical significance. The overall highest mutation rate in both BRCA1/2-mutated and non-mutated were TP53 (80.6% and 73.1%, p = 0.2659). Differences were also noted between BRCA1/2-mutated and non-mutated specimens by NGS in APC (6.3% versus 1.9%, p = 0.0644) and PIK3CA (47.6% versus 59.6%, p = 0.0041), with both trends reaching statistical significance.

Table 2: NGS results of BRCA1/2-mutated and non-mutated samples. The highest overall mutation rates in both subtypes were biomarkers like TOPO1 (63.5% and 63.4%), EGFR (65.2% and 67.4%), and the immune checkpoint L1CAM biomarker, PO-L1 (51.1% and 51.9%), with non-statistically significant differences. Differences noted between BRCA1/2-mutated and non-mutated specimens were detected by IHC in AR (11.1% versus 22.0%, p = 0.0309) and PTEN (47.6% versus 59.6%, p = 0.0041), with both trends reaching statistical significance.

Figure 4 – In situ hybridization in BRCA1/2-mutated and non-mutated samples. Of note, PIK3CA mutations were significantly lower in BRCA1/2-mutated specimens compared to non-mutated specimens (11.1% versus 25.8%, p = 0.0137). APC trended higher in the BRCA1/2-mutated versus non-mutated group (6.3% versus 1.9%, p = 0.0644).

Conclusions:

• Multi-omic profiling can identify differences in the underlying biology of TNBC, particularly between TNBC with and without BRCA1/2 mutations.

• Higher PIK3CA mutation rates in the non-BRCA1/2-mutated TNBC cohort warrants further investigation in clinical trials, particularly in a population with historically worse survival rates in comparison to BRCA1/2-mutated populations.

• Biomarkers like AR deserve further study to assess whether a subgroup of non-BRCA1/2 TNBC may derive benefit from hormonal agents.

References:


