Biomarker comparison between androgen receptor – positive-triple-negative breast cancer (AR+TNBC) and quadruple-negative breast cancer (QNBC)

**Background**

Although AR lacks hormone receptors traditionally associated with breast cancer, emerging data suggest that AR plays a strong role in the biology of TNBC and drives a distinct subtype of breast cancer, termed AR+TNBC. Recent studies have reported that AR+TNBC tumors are significantly younger than patients with low expression of TS, TUBB3 and high expression of TLE3. This suggests that for AR+TNBC tumors, future clinical trial design can consider the use of antiandrogen therapies. On the other hand, clinical trials for immune checkpoint inhibitors in AR+TNBC tumors have shown limited success, potentially increasing the need for targeted therapies.

**Methods**

Tumors were analyzed using formalin-fixed paraffin-embedded (FFPE) tumor samples using commercially available detection kits, automated staining techniques (Benchmark XT, Ventana, and Autostained L1 4E1, Dako), and commercially available antibodies. FISH was performed using fluorescent in situ hybridization, or FISH (EGFR, HER2, TOP2A, and P53) and sequencing (Next-generation sequencing, or NGS and Sanger). Tumors were categorized into three main groups: AR+TNBC tumors as defined by IHC staining, AR-unknown tumors, and QNBC tumors.

**Results**

**Figure 1: Patient characteristics**

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Average</th>
<th>Interquartile Range</th>
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<tbody>
<tr>
<td>AR+TNBC</td>
<td>59.2</td>
<td>52-68</td>
</tr>
<tr>
<td>QNBC</td>
<td>54.9</td>
<td>47-63</td>
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**Figure 2: IHC and ISH marker comparison between AR+TNBC and QNBC.** Bars represent the frequency of mutations observed in the two cohorts. Arrows indicate that the difference is statistically different (p<0.05) with the corresponding p values labeled. The arrows represent the percentage of patients with positive AR expression.

**Figure 4: Gene mutations with similar frequencies in AR+TNBC and QNBC.** No mutations were observed in AUK, GNA11, MAP4, or MPN. Bars represent the frequency of biomarker mutations in the two cohorts.

**Conclusions**

- **In** a cohort of 5525 TNBC tumors, AR expression was seen in 17.4% of cases, while 83.6% of TNBC were categorized as QNBC tumors.
- Patients with AR+TNBC tumors are significantly younger than patients with QNBC tumors.
- PD-1 expression is significantly enriched in QNBC tumors compared to AR+TNBC, suggesting activation of this immune suppressive pathway in hormone-independent breast tumors.
- Overexpression of EGFR, TOP2A and loss of Pten expression are more prevalent in QNBC, suggesting additional therapeutic options for QNBC.
- Combinatorial strategies with these agents and anti-androgen therapies warrant further study in clinical trials.

**References**

1. Joanne Xiu, PhD; Elisa Obied, MD; Zoran Gatalica, MD, Dsc; Sandeep Reddy, MD; Lori J. Goldstein, MD; John Link, MD; James Waisman, MD; Caris Life Sciences, Phoenix, AZ; Fox Chase Cancer Center, Philadelphia, PA; Breastlink Medical Group, Orange, CA; City of Hope Medical Oncology, Duarte, CA

