An immune gene signature as a predictor of chemosensitivity in ER+, HER2- breast cancer

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Introduction
Gene expression signatures (GES) have shown promise as predictors for response to neoadjuvant chemotherapy in early breast cancer (BC). However, fewer data are available on ER+/HER2- breast cancer, while their role in the metastatic setting is undefined. This study aimed to explore their role as predictive biomarkers in ER+/HER2- BC.

Methods
A fine needle aspiration biopsy was obtained prior to the initiation of first line chemotherapy from patients enrolled to the phase 3 TEX trial of epirubicin and paclitaxel with or without capetaxel. Gene modules related to immune response (immune module score; IMS), proliferation, ER signaling and recurring genetic alterations were analyzed for association with objective response to chemotherapy. The results of IMS were then validated in biopsies obtained from patients enrolled to the phase 2 PROMIX trial of six cycles of neoadjuvant epirubicin and docetaxel, plus bevacizumab for cycles 3-6, both at baseline and after short-term exposure to chemotherapy (2 cycles).

Results
At the metastatic setting, GE data were available for 109 patients (cohort A; Table 1 and figure 1). Objective response to chemotherapy was statistically significantly associated with IMS (odds ratio (OR): 3.62, 95% CI: 1.03–2.64; P=0.04). Subgroup analysis showed that this association was restricted to patients with ER positive tumors (OR=2.23, 95% CI 1.21 – 4.48; P=0.01, P for interaction 0.04). No statistically significant associations were noted between objective response rate and the other GES (figure 2). Of the 113 ER+/HER2- BC patients enrolled in the PROMIX trial, GE data at baseline were available for n=71 (cohort B) and longitudinally at baseline and after cycle 2 for n=49 (cohort C). Baseline IMS was predictive for pCR (OR: 2.29, 95% CI 1.05 – 5.38, P=0.037) and decrease in tumor size (r=0.25, P=0.047) (figure 3). Moreover, IMS at cycle 2 but not IMS at baseline was statistically significant in a multivariate analysis (P=0.004).

Conclusions
In the correlative analyses of two prospective trials, immune response was found to predict chemosensitivity in both the neoadjuvant and metastatic settings. Moreover, short term exposure to chemotherapy accentuated this effect, suggesting a priming of anti-tumor immunity due to the release of neoantigens. These could have important implications in the selection of patients for chemotherapy and as candidates for trials evaluating combined chemoinmunotherapy.

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Cohort A N=109</th>
<th>Cohort B N=71</th>
<th>Cohort C N=49</th>
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<tbody>
<tr>
<td>Median (range)</td>
<td>49 (27 – 69)</td>
<td>49 (27 – 69)</td>
<td>50 (27 – 69)</td>
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<tr>
<td>LN Status</td>
<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>N/A</td>
<td>41 (58%)</td>
<td>29 (39.1%)</td>
</tr>
<tr>
<td>Negative</td>
<td>N/A</td>
<td>17 (24%)</td>
<td>10 (20.4%)</td>
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<tr>
<td>AIMS Subtype</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Luminal A</td>
<td>3 (2.7%)</td>
<td>15 (21.1%)</td>
<td>8 (16.3%)</td>
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<tr>
<td>Luminal B</td>
<td>48 (44%)</td>
<td>21 (29.5%)</td>
<td>18 (36.7%)</td>
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<tr>
<td>HER2 enriched</td>
<td>11 (15.5%)</td>
<td>11 (22.4%)</td>
<td></td>
</tr>
<tr>
<td>Basal-like</td>
<td>21 (19.2%)</td>
<td>5 (7%)</td>
<td>10 (20.2%)</td>
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<tr>
<td>Normal-like</td>
<td>5 (4.6%)</td>
<td>20 (28.1%)</td>
<td>7 (14.2%)</td>
</tr>
</tbody>
</table>

Figure 1. CONSORT diagrams of the two studies

Figure 2. Association of ORR and IMS (A); immune module 2 (B); Proliferation (C); ER signaling (D); PIK3CA (E); TP53 (F) modules. Only the immune modules and only in ER positive disease predicted ORR at the metastatic setting

Figure 3. Association of pCR and baseline IMS (A); decrease in tumor size and baseline IMS (B); decrease in tumor size and IMS at cycle 2 (C)

References
1. Foukakis et al. BJC 2018
2. Matikas et al. submitted manuscript
4. Pepe et al JNCG 2014

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