Comprehensive Genomic Profiling (CGP) of metastatic Invasive Lobular Carcinoma reveals heterogeneity in immune biomarkers and resistance alterations across biopsy sites

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ABSTRACT

Introduction

Metastatic breast cancer is a clinically challenging disease with poor outcomes. Invasive lobular carcinoma (ILC) is a rare subtype of breast cancer with distinct patterns of metastasis, including frequent gastrointestinal (GI) and female reproductive (FR) metastases (1). Due to their relative rarity, ILC is known about the genomic characteristics of ILC across all sites. Here we explore the genomic landscapes of 109 ILC samples across ILCs, stratified by site, with an examination of immune checkpoint inhibition (ICI) biomarkers, therapeutic alterations, and resistance mutations.

RESULTS

Table 1. Prevalence of met-enzalutin alterations in breast-biopsied ILC/DCD, metastatic DCID/ILC and ILC metastases broken down by site. Shown are all genes alteration classes that are significantly enriched in metastatic ILC overall or at least one met site, relative to breast ILC. Mut indicates short variant alterations and RE indicates rearrangement/fusion events. * indicates significance vs breast ILC for each site.

<table>
<thead>
<tr>
<th>Gene Alteration Class</th>
<th>Overall ILC</th>
<th>Metastatic ILC</th>
<th>Breast ILC</th>
<th>p-value ILC vs Breast ILC</th>
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</thead>
<tbody>
<tr>
<td>Total alterations</td>
<td>72,826</td>
<td>36,859</td>
<td>35,967</td>
<td>0.0001**</td>
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<tr>
<td>Mutations</td>
<td>25,684</td>
<td>13,986</td>
<td>11,704</td>
<td>0.0001**</td>
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<tr>
<td>Rearrangements</td>
<td>47,142</td>
<td>17,211</td>
<td>24,254</td>
<td>0.0001**</td>
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<tr>
<td>fusions</td>
<td>44,944</td>
<td>11,324</td>
<td>33,620</td>
<td>0.0001**</td>
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<tr>
<td>INDELs</td>
<td>7,882</td>
<td>2,665</td>
<td>5,217</td>
<td>0.0001**</td>
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<tr>
<td>SNPs</td>
<td>55,944</td>
<td>14,394</td>
<td>41,550</td>
<td>0.0001**</td>
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</tbody>
</table>

Conclusions

CGP revealed significant heterogeneity in ILC met across tissues. ICP biomarkers were variable across sites with the highest frequency in ILC-GI sites, potentially offering additional treatment avenues for these tumors. Potentially targetable alterations in PKNGA were common in ILC met with high prevalence across sites, potentially useful targets for PKNGA inhibitors. Therapy-resistance alterations were common in ILC met breast cancers across sites. Notably, BRD4B alterations were most prevalent in ILC liver met, but were common at other sites. The high prevalence of therapeutic and resistance alterations suggests value in profiling metastatic lesions.

MATERIALS AND METHODS

Comprehensive genomic profiling (CGP) workflow

CGP was carried out at Foundation Medicine with hybrid-capture for exons from up to 339 cancer-related genes plus a small number from up to 11 genes (PTEN/MAPK/ERBB2). Tumor mutational burden (TMB) was determined on the 0.8-1.1 Mb (MIT, 298424412). Vardiance PD-L1 staining (PD-L1; positive = 1 staining) was available for a subset of samples. 1021 breast-biopsied ILC and 9524 breast-biopsied and 1057 met-biopsied ILC were available for analysis.

Figure 1. Biomarkers of immune checkpoint inhibitor response differ across ILC met sites. (A) Fraction of patients with tumor mutational burden greater or equal to 10 tumors/million is shown for all ILC met and ILC metectases stratified by site. (B) VHN- TMAID GP/ILC, DCD, ILC, DOL, positivity rates are shown across sites. The highest biomarker prevalence is observed in GI and skin ILC metastases.

Figure 2. Prevalence of potentially actionable alterations across sites. (A) PKNGA short variant alteration prevalence is similarly high across met sites. (B) PKNGA/ICD17 preva- lence differs across sites with the highest prevalence in female reproductive ILC met and lowest prevalence in GI ILC met.

Figure 3. Landscape of alteration prevalence in local ILC (breast biopsied) and meta- static ILC. Shown are all genes alterations that are significantly enriched in metastatic ILC overall or at least one metastatic site, relative to breast-biopsied ILC.

Figure 4. Frequency of met-enzalutin alterations across sites. Pictorial are the fraction of samples with at least one met-enzalutin-enriched (MET) alteration (Table 1). Female reproductive tumors exhibited the lowest prevalence of ME alterations, while liver met had the highest prevalence.

Figure 5. Prevalence of select met-enzalutin alterations across ILC met- satatic sites. Met-enzalutin heterogeneity is observed in ERBB2/ERBB1-AF11, and RBB1.

CONCLUSIONS

- ICP biomarkers were variable across sites with the highest frequency in ILC gastrointestinal met, potentially offering additional treatment avenues.
- Alterations in PKNGA were common in ILC met with high prevalence across sites, suggesting potential broad utility for PKNGA inhibitors.
- Therapy-resistance alterations were common in ILC met but varied across sites, with ERBB2 mutations most prevalent in ILC liver met.
- RBB1 mutations are associated with CDK4/6 resistance and were highest in gastrointestinal and skin sites.