BACKGROUND

• There is a need for predictive & prognostic biomarkers & an in-depth investigation of immune response & resistance with ICIs.

• Published biomarkers have primarily been conducted in the context of clinical trials limiting generalizability to a “real world” setting.

• Using Oncology Research Information Exchange Network (ORIEN) Avatar® real world clinical, genomic and transcriptomic data conducted under the Total Cancer Care protocol we investigated predictive biomarkers of ICI benefits in pts with advanced malignancies focusing on RNA-seq data for this analysis.

METHODS

• Clinical data were normalized as part of ORIEN Avatar®.

• RNA-seq was performed on tumor samples following the RSEM pipeline and gene expressions were quantified as Transcript Per Million (TPM).

• Gene expressions (GE) were log2(TPM+1) transformed.

• 28 previously published GE signatures were tested in pan-cancer cohorts.

• Overall Survival (OS) was the primary endpoint.

• Mann-Whitney U test was used to compute differences between groups, and Kaplan-Meier survival analysis was performed. Test with p<0.05 was considered statistically significant.

• Z-score was generated to compare responders and non-responders based on area under the receiver operating curve (AUROC).

RESULTS

• 659 patients treated with ICI for kidney cancer (n = 151), lung cancer (n = 138), melanoma (n = 123), head and neck cancer (n = 121), sarcoma (n = 78) and bladder cancer (n = 48) were included.

• ICI regimens: Atezolizumab, avelumab, cemiplimab, nivolumab, pembrolizumab and ipilimumab+nivolumab.

• We defined “good” and “poor” outcomes if OS was >24 or < 24 months, respectively (Table 1).

• Twelve immune active gene signatures were associated with ICI responses in melanoma (p < 0.05); Figure 1 & Tables 2.

• An angiogenesis signature (p = 0.0281) and a tertiary lymphoid structure signature (p= 0.0133) were associated with ICI responses in kidney cancer and head and neck cancer, respectively; Figure 1 & Tables 2.

• None of the 28 evaluated gene signatures were associated with ICI responses in lung cancer, bladder cancer or sarcoma; Figure 1.

CONCLUSIONS

• We validated the predictive value of immune related gene signatures in melanoma, kidney and head and neck cancers utilizing RWD.

• Ongoing analyses are taking on a discovery approach for predictive genes and related pathways to better understand the underlying mechanisms related to tumor immunomicrogically across the different tumor types.

Table 1. Patients with OS ≥ 24 months are marked as responders

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Patients</th>
<th>Responders</th>
<th>Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>48</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>HNSCC</td>
<td>121</td>
<td>22</td>
<td>99</td>
</tr>
<tr>
<td>Kidney</td>
<td>151</td>
<td>106</td>
<td>45</td>
</tr>
<tr>
<td>Lung</td>
<td>138</td>
<td>33</td>
<td>105</td>
</tr>
<tr>
<td>Melanoma</td>
<td>123</td>
<td>72</td>
<td>51</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>78</td>
<td>14</td>
<td>64</td>
</tr>
</tbody>
</table>

Table 2. Signatures with significant correlation with survival (>24 vs. <24 months)

<table>
<thead>
<tr>
<th>Gene Signature</th>
<th>Reference</th>
<th>P-Value</th>
<th>Cancer</th>
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</thead>
<tbody>
<tr>
<td>Tertiary Lymphoid Structures</td>
<td>Cabrita 2020</td>
<td>0.0133</td>
<td>Head &amp; Neck</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Cristescu 2022</td>
<td>0.0281</td>
<td>Renal</td>
</tr>
<tr>
<td>IFNg/Effecter T-cell</td>
<td>Fehrenbacher 2016</td>
<td>0.001</td>
<td>Melanoma</td>
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<tr>
<td>Effecter T-cell</td>
<td>Bolen 2011</td>
<td>0.0014</td>
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<tr>
<td>IFNg-5</td>
<td>Ayers 2017</td>
<td>0.0017</td>
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<tr>
<td>Immune Cytolytic Activity</td>
<td>Rooney 2015</td>
<td>0.002</td>
<td>Melanoma</td>
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<tr>
<td>IFNg expanded immune 18</td>
<td>Ayers 2017</td>
<td>0.0035</td>
<td>Melanoma</td>
</tr>
<tr>
<td>TIP Hot</td>
<td>Wang 2021</td>
<td>0.004</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Cytotoxic Immune Signature</td>
<td>Davoli 2017</td>
<td>0.0047</td>
<td>Melanoma</td>
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<tr>
<td>Tertiary Lymphoid Structures</td>
<td>Chaurio 2022</td>
<td>0.0061</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Chemokine</td>
<td>Coppola 2011, Mule 2012</td>
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<td>T &amp; B cell Interplay</td>
<td>Tarhini 2017</td>
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<td>Roh Immune Score</td>
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<td>MHC-II</td>
<td>Liu 2021</td>
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