Clinical, Pathologic and Genomic Profiles of Exceptional Responders to Anti-PD1 Therapy in Renal Cell Carcinoma

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PD-1 Checkpoint Blockade in RCC

• The efficacy of PD-1/PDL-1 blockade in RCC has been demonstrated in multiple trials.

• Objective response rates range from 20-30%.

• A minority of patients achieves durable response

McDermott 2015
Durable Response

Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody

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Durable, partial response for 3 years → ongoing complete response
Predictors of Response

• Previous studies have correlated response to PD-1 blockade with:
  • Tumor PD-L1 expression (Topalian 2012)
    • Not seen in recent phase III trial (Motzer 2015)
  • Somatic mutation burden (Snyder 2014, Rizvi 2015)
  • DNA mismatch repair defects (Le 2015)
  • Cell-mediated immune transcripts (Choueiri ASCO 2015)

• No studies have examined predictors of durable response.
Study Design

• What predicts long-term, durable response to anti-PD1 therapy?

• Design: Study the two extreme phenotypes
  • Patients with complete-response (CR) by RECIST or a near-complete response (defined as a PET complete response and 10% or less stable residual disease) at 24 months “Exceptional responders” – (n=4)
  • Primary refractory (n=3)

• Clinical, pathologic characteristics
  • Tumor expression of PDL1
  • Infiltrating CD8+ lymphocytes

• Whole exome sequencing
  • Number of mutations
  • Number of putative of neoantigens

• RNA expression (Nanostring)
Changes in target lesions diameter in RCC patients treated with anti-PD-1 therapy.
# Clinical Characteristics

<table>
<thead>
<tr>
<th>ECOG PS</th>
<th>Primary tumor stage</th>
<th>Time to Metastasis (m)</th>
<th>Site of metastasis</th>
<th>Prior Systemic Therapy</th>
<th># Prior Therapies</th>
<th>Survival from initiation of PD1 Therapy (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exceptional Responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>pT3bNxMx</td>
<td>27.0</td>
<td>Lung</td>
<td>HDAC inhibitor.</td>
<td>2</td>
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<tr>
<td><strong>Median Exceptional Responder</strong></td>
<td>1</td>
<td></td>
<td>14.4</td>
<td></td>
<td></td>
<td>3</td>
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<tr>
<td><strong>Median Primary refractory</strong></td>
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<td></td>
<td>7.8</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.7</td>
<td></td>
<td>0.7</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>pT2bNxMx</td>
<td>7.8</td>
<td>Lung</td>
<td>IL-2</td>
<td>1</td>
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</tbody>
</table>
### IHC Analysis

#### PDL1 (+)

<table>
<thead>
<tr>
<th>Exceptional responders</th>
<th>Primary refractory</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td><strong>Tumor PD-L1 Expression, n(%)</strong></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Absent</td>
<td>1 (25)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Present</td>
<td>3 (75)</td>
<td>2 (67)</td>
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<tr>
<td><strong>Immune cell infiltrate PD-L1 Expression (n=6), n(%)</strong></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Absent</td>
<td>2 (67)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Present</td>
<td>1 (33)</td>
<td>1 (33)</td>
</tr>
</tbody>
</table>

#### PDL1 (-)
IHC Analysis

<table>
<thead>
<tr>
<th></th>
<th>Exceptional responders</th>
<th>Primary refractory</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD8+ Intratumor lymphocytes/hpf (mean) (n=6)</strong></td>
<td>126.7</td>
<td>28.8</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>CD8+ stromal lymphocytes/hpf (mean) (n=6)</strong></td>
<td>211.8</td>
<td>70.6</td>
<td>0.2</td>
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</tbody>
</table>
Somatic Mutational Density

Exceptional Responders: 67
Primary Refractory: 35

TCGA (all ccRCC): 50
TCGA (M1): 48
Complete responders had a higher proportion of mutated chromatin remodeling genes \textit{PBRM1} (75\% vs 33\%) and \textit{SETD2} (75\% vs 0).
Neoantigen Prediction

**Neoantigens:**
21-amino-acid polypeptides centered on mutated residues were scanned and processed with netMHC. < 500 nm affinity considered putative neoantigens.

**Mutation-associated neoantigens (MANA):**
Neoantigens with strong binding (<50 nm) with complementary wild type with weak or no binding.
RNA Expression

Nanostring RNA Expression Cancer Immune Panel: 770 genes
31 genes differentiated ER and Primary Refractory

Extreme Responders:
- Acute inflammatory: IL-6, CXCL5, CXCL2
- T cell activation: IL2RA

Primary Refractory
- T cell inhibition: TNFRSF14, CCL24

All p < 0.05, FDR < 0.1
Summary

• Patients with long-term CR to anti-PD1 therapy have trends toward:
  • Increased mutational density
  • Increased mutation-associated neoantigens
  • Increased CD8 infiltrate
  • Increased expression of proinflammatory cytokines

• Future directions:
  • Multi-institutional collaborations to examine exceptional response
  • *In vitro* confirmation of neoantigen-MHC interaction
  • Validation of immune signatures in prospective trial
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