Genomic and Transcriptomic Predictors of Response to First-Line Treatment with Ipilimumab and Nivolumab in patients with Metastatic Clear Cell Renal Cell Carcinoma

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Background

- Ipilimumab and nivolumab is a standard of care systemic treatment in patients with IMDC intermediate/poor risk metastatic clear cell renal cell carcinoma (mRCC)\(^1\)

- Genomic and transcriptomic biomarkers such as TMB, PBRM1 alterations and T-effector gene expression signature are associated with response to immunotherapy regimens\(^2-6\)

- In this study we aimed to explore genomic and transcriptomic biomarkers associated with disease control rate (DCR) to ipilimumab and nivolumab therapy in patients with mRCC

\(\text{References:}\)
\(^1\) Motzer RJ, Nizar, M. et.al. NEJM 2018;
\(^4\) Chowell D, Morris LGT, et al. Science 2018;
Methods

Eligibility:
- Clear cell mRCC
- IMDC intermediate/poor risk
- First-line ipilimumab and nivolumab

DNA profiling
- DCR n=33
- no-DCR n=16

RNA profiling
- DCR n=10
- no-DCR n=4

DCR, disease control rate
## Results

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Disease Control (n=33)</th>
<th>No Disease Control (n=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Diagnosis</strong> (median, years)</td>
<td>60</td>
<td>64</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75.8%</td>
<td>75%</td>
<td>0.30</td>
</tr>
<tr>
<td>Female</td>
<td>24.2%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>84.9%</td>
<td>87.5%</td>
<td>0.32</td>
</tr>
<tr>
<td>Non-white</td>
<td>15.1%</td>
<td>12.5%</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 30</td>
<td>42.4%</td>
<td>25%</td>
<td>0.77</td>
</tr>
<tr>
<td>More than 30</td>
<td>57.6%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42.4%</td>
<td>25%</td>
<td>0.57</td>
</tr>
<tr>
<td>No</td>
<td>57.6%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td><strong>Nephrectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>69.7%</td>
<td>81.2%</td>
<td>0.46</td>
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<tr>
<td>No</td>
<td>30.3%</td>
<td>18.8%</td>
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<tr>
<td><strong>Sarcomatoid</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.1%</td>
<td>12.5%</td>
<td>0.19</td>
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<tr>
<td>No</td>
<td>90.9%</td>
<td>87.5%</td>
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</tr>
<tr>
<td><strong>IMDC Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>93.9%</td>
<td>87.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poor</td>
<td>6.1%</td>
<td>12.5%</td>
<td></td>
</tr>
</tbody>
</table>
Results

Genomic Alteration Frequency

Genomic alteration frequency between the groups were not statistically significant
Results

Genomic expression analysis

- 51 genes were differentially expressed (q<0.1).
- 40 genes were overexpressed in DCR, while 11 genes were overexpressed in the no-DCR.
Results

Disease Control

- E2F Targets (q=0.02)
- G2M Checkpoint (q=0.09)
- MYC Targets V2 (q=0.03)
- Estrogen Response Late (q=0.01)

No disease Control

- TGF-beta signaling (q=0.01)
Limitations

▪ Retrospective nature
▪ Small sample size

Conclusions

▪ Our hypothesis generating data suggest that transcriptomic analysis may help in:
  ✔ Patient selection
  ✔ Treatment selection
  ✔ Patient prognostication
  ✔ Patient counseling
▪ The results of our study warrants external validation
Acknowledgements

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