CHARACTERIZING **RECURRENT** AND **LETHAL** SMALL RENAL MASSES IN CLEAR CELL RENAL CELL CARCINOMA USING RECURRENT SOMATIC MUTATIONS

Brandon Manley, Ed Reznik, Maria Becerra, Jozefina Casuscelli, Daniel Tennenbaum, Mazyar Ghanaat, Mahyar Kashan, Almedina Redzematovic, Yusuke Sato*, Maria Arcila, Martin Voss, Darren Feldman, Robert Motzer, Paul Russo, Jonathan Coleman, James Hsieh and Ari Hakimi

*Department of Urology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
Introduction

• Patients presenting with small renal masses (SRMs) are a commonly encountered clinical entity, the most common histology among these tumors is clear cell renal cell carcinoma (ccRCC)

• While relatively rare, in some patients these can be lethal tumors and present with metastatic disease

• Selected patients with SRMs may be appropriate for active surveillance (AS)

• Current AS algorithms largely rely on patient characteristics, growth parameters and histology

• We sought to identify genomic biomarkers that could augment the management of SRMs, including those being evaluated for AS
Methods

• We identified ccRCC tumors ≤4cm with genomic sequencing data on primary tumors from:
  • The Cancer Genome Atlas (n=110)
  • University of Tokyo (n=38)
  • The International Cancer Genome Consortium (n=32)
  • Memorial Sloan Kettering Cancer center (n=25)

• Exclusions: multiple kidney tumors, no path size, known syndrome

• Total of 205 patients
## Mutational Frequency $\geq 5%$

<table>
<thead>
<tr>
<th>Mutation</th>
<th># Patient w/ Mutation</th>
<th>Frequency of mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VHL</strong></td>
<td>129</td>
<td>62.90%</td>
</tr>
<tr>
<td><strong>PBRM1</strong></td>
<td>68</td>
<td>33.20%</td>
</tr>
<tr>
<td><strong>SETD2</strong></td>
<td>20</td>
<td>9.80%</td>
</tr>
<tr>
<td><strong>BAP1</strong></td>
<td>15</td>
<td>7.30%</td>
</tr>
<tr>
<td><strong>KDM5C</strong></td>
<td>14</td>
<td>6.80%</td>
</tr>
<tr>
<td><strong>mTOR</strong></td>
<td>14</td>
<td>6.80%</td>
</tr>
</tbody>
</table>
Recurrence and Lethality

- Number of patients that recurred or died of their disease = 25 of 205 (12.1%)
- 13 patients presented with Stage IV disease, 10/13 died of their disease.
- Median follow up of remaining cohort = 3.6 years (43.1 months)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Enrichment in tumors with recurrence or death?</th>
<th>Survival Analysis P-Value</th>
<th>Enrichment is tumors with recurrence or death? (adjusted)</th>
<th>Survival Analysis P-Value (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL</td>
<td>1.00</td>
<td>0.880</td>
<td>1.00</td>
<td>0.87</td>
</tr>
<tr>
<td>PBRM1</td>
<td>0.113</td>
<td>0.274</td>
<td>0.170</td>
<td>0.4111</td>
</tr>
<tr>
<td>SETD2</td>
<td>0.021</td>
<td><strong>0.037</strong></td>
<td>0.063</td>
<td>0.111</td>
</tr>
<tr>
<td>BAP1</td>
<td>0.093</td>
<td>0.070</td>
<td>0.170</td>
<td>0.139</td>
</tr>
<tr>
<td>KDM5C</td>
<td><strong>0.003</strong></td>
<td><strong>&lt;0.001</strong></td>
<td><strong>0.016</strong></td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>MTOR</td>
<td>0.387</td>
<td>0.436</td>
<td>0.463</td>
<td>0.523</td>
</tr>
</tbody>
</table>
KDM5C
## Recurrence and Lethality Stage I-III only

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Enrichment in tumors with recurrence or death? Fischer Exact</th>
<th>Survival Analysis P-Value Log-Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL</td>
<td>0.579</td>
<td>0.569</td>
</tr>
<tr>
<td>PBRM1</td>
<td>0.086</td>
<td>0.194</td>
</tr>
<tr>
<td>SETD2</td>
<td><strong>0.031</strong></td>
<td><strong>0.047</strong></td>
</tr>
<tr>
<td>BAP1</td>
<td>0.601</td>
<td>0.929</td>
</tr>
<tr>
<td>KDM5C</td>
<td><strong>0.033</strong></td>
<td><strong>0.010</strong></td>
</tr>
<tr>
<td>MTOR</td>
<td>0.269</td>
<td>0.431</td>
</tr>
</tbody>
</table>
KDM5C

Stage I-III only
SETD2

Stage I-III only
Conclusions

• We identified potential mutations in SRMs that are associated with recurrence and lethality
• The strongest association was seen in those with $KDM5C$ mutations
• A trend towards significance was also seen in those with $SETD2$ mutations and less so in those with $BAP1$ mutations
• Retrospective analysis is restricted by the limited sample size and small number of events
• Prospective studies needed to evaluate these markers in the stratification and selection of patients, especially those for AS
Thank you

**Biostatistics**
Emily Zabor
Emily Vertosick
Elli Papaemmanuil
Andrew Vickers
Dan Sjoberg
Mithat Gonen
Irina Ostrovnaya
Venkat Seshan
Ronglai Shen

**HOPP**
James Hsieh
Jozefina Casucelli
Daniel Tennenbaum
Maria Becerra
Dina Djesevic
Yiyu Dong
Joe Lee
Emily Cheng
Yogesh Ganesan
Song Han

**Computational Biology**
Ed Reznik
Chris Sander

**Immunology**
Ming Li
Ming Lui

**Radiology**
Evis Sala
Herbert Vargas
Hedi Hricak
Kayvan Keshari
Omer Aras
Jeremy Durack

**GU Oncology**
Bob Motzer
James Hsieh
Maria Carlo
Martin Voss
Darren Feldman
Joe Lee

**Pathology**
Victor Reuter
Yingbei Chen
Mike Berger
Satish Tickoo
Chris Iacobuzio

**Urologic Surgery**
Ari Hakimi
Paul Russo
Nicole Benfante
J. Coleman
**BAP1 (all stages)**

![Graph showing survival probability over time for BAP1 (all stages)]