Disclosure

Novartis
Pfizer
Eisai
Chugai
Cancer Genomics Inc.
Differential Overall Survival Results in RECORD-3 Study Based on Three Distinct Clear Cell Metastatic Renal Cell Carcinoma Molecular Subgroups Classified by BAP1 and/or PBRM1 Mutations

James J. Hsieh, David Chen, Patricia I. Wang, Ying-Bei Chen, Mahtab Marker, Parul Patel, Umesh Bhanot, Michael Berger, Emily H. Cheng, Jennifer Knox, Martin H. Voss, Maurizio Voi, Robert J Motzer
Treatment for ccRCC (Past, Now, Future)

- **High dose interleukin-2**
- **Interferon-α**
- **Sorafenib**
- **Sunitinib**
- **Temsotinilumis**
- **Everolimus**
- **Bevacizumab + IFN**
- **Pazopanib**
- **Axitinib**
- **Everolimus**
- **Nivolumab**
- **Cabozantinib**
- **Lenvatinib**

**Dark Age**
1992-2005

**Modern Age**
- **Single Arm Targeted Therapy 2005-2015**

**Golden Age**
2015-2016
- New Drugs: Ipilimumab etc.
- Precision
- Combinations
- Sequences
- Vaccination

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November 4-5, 2016
Marriott Miami Biscayne Bay, Miami, Florida, USA

www.kidneycancersymposium.com
RECORD-3 Study Design, Primary Results, & NGS of ccRCC (220)

**Study endpoints**
- Primary
  - PFS – 1st-line noninferiority of everolimus to sunitinib
- Key Secondary
  - PFS – combined
  - OS
  - Safety

**Primary endpoint analysis:**
Median PFS first-line (mo)

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.9</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Hazard Ratio = 1.4
2-Sided 95% CI [1.2–1.8]


OS, overall survival; PFS, progression-free survival.
Mutations above 10% in Metastatic ccRCC

<table>
<thead>
<tr>
<th>Gene</th>
<th>RECORD-3 (n=220)</th>
<th>TCGA (n=417)</th>
<th>Sato 2013 (n=240)</th>
<th>Haikimi 2013 (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL</td>
<td>75% (n=164)</td>
<td>52%</td>
<td>82%</td>
<td>49%</td>
</tr>
<tr>
<td>PBRM1</td>
<td>46% (n=101)</td>
<td>33%</td>
<td>41%</td>
<td>29%</td>
</tr>
<tr>
<td>SETD2</td>
<td>30% (n=65)</td>
<td>12%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>BAP1</td>
<td>19% (n=42)</td>
<td>10%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>KDM5C</td>
<td>15% (n=32)</td>
<td>7%</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>PTEN</td>
<td>12% (n=26)</td>
<td>4%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Record-3 ccRCC: PFS1L Genomic Biomarkers & SUN/EVE Correlation

PBMR1 MT: SUN=EVE

BAP1 MT: Bad, esp on EVE

KDM5C MT: Well on SUN

PBMR1 Mutants on SUN or EVE

BAP1 Mutants on SUN or EVE

KDM5C Mutants on SUN or EVE

PBMR1 MT (Everolimus) – PBMR1 WT (Everolimus)
PBMR1 MT (Sunitinib) – PBMR1 WT (Sunitinib)

BAP1 MT (Everolimus) – BAP1 WT (Everolimus)

KDM5C MT (Everolimus) – KDM5C WT (Everolimus)
KDM5C MT (Sunitinib) – KDM5C WT (Sunitinib)


### Median OS and Biomarker Mutation Status

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>First-Second Line Treatment</th>
<th>Population</th>
<th>Patients, n</th>
<th>Events, n</th>
<th>OS, median (95% CI), months</th>
<th>Hazard Ratio (95% CI)</th>
<th>Raw Log-Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PBRM1</strong></td>
<td><strong>Sunitinib-Eve</strong></td>
<td>Wild Type</td>
<td>55</td>
<td>36</td>
<td>32.4 (19.2-38.6)</td>
<td>0.73 (0.45-1.19)</td>
<td>0.3491</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutant</td>
<td>56</td>
<td>35</td>
<td>31.7 (23.1-37.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Everolimus-Sun</strong></td>
<td>Wild Type</td>
<td>64</td>
<td>46</td>
<td>16.2 (10.7-26.9)</td>
<td>0.50 (0.30-0.84)</td>
<td>0.0038</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutant</td>
<td>45</td>
<td>24</td>
<td>39.6 (34.0-NE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BAP1</strong></td>
<td><strong>Sunitinib-Eve</strong></td>
<td>Wild Type</td>
<td>91</td>
<td>58</td>
<td>33.2 (22.7-37.8)</td>
<td>1.38 (0.71-2.68)</td>
<td>0.4578</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutant</td>
<td>20</td>
<td>13</td>
<td>29.9 (8.9-NE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Everolimus-Sun</strong></td>
<td>Wild Type</td>
<td>87</td>
<td>54</td>
<td>34.0 (18.1-41.5)</td>
<td>1.53 (0.85-2.77)</td>
<td>0.1128</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutant</td>
<td>22</td>
<td>16</td>
<td>9.8 (8.2-22.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KDM5C</strong></td>
<td><strong>Sunitinib-Eve</strong></td>
<td>Wild Type</td>
<td>90</td>
<td>63</td>
<td>31.4 (22.0-34.5)</td>
<td>0.39 (0.18-0.88)</td>
<td>0.0209</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutant</td>
<td>21</td>
<td>8</td>
<td>NE (25.8-NE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Everolimus-Sun</strong></td>
<td>Wild Type</td>
<td>98</td>
<td>64</td>
<td>23.7 (15.8-31.2)</td>
<td>0.55 (0.23-1.30)</td>
<td>0.1594</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutant</td>
<td>11</td>
<td>6</td>
<td>40.3 (5.1-NE)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; MT, mutant; NE, nonestimable; WT, wild-type.

BAP1 and PBRM1 Mutations
Mutual Exclusivity and 3 Molecular Subgroups

• Group 1: BAP1 MT, PBRM1 WT/MT: 19%
• Group 2: BAP1 WT, PBRM1 MT: 43%
• Group 3: BAP1 WT, PBRM1 WT: 38%
OS and BAP1/PBRM1 Mutations-based 3 Molecular Subgroups

OS outcomes within each randomized treatment arm varied by molecularly defined subgroups

SUN-EVE

EVE-SUN

BAP1 vs PBRM1 groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Median OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAP1 Gr. BAP1 MT &amp; PBRM1 WT/MT</td>
<td>20</td>
<td>29.9</td>
<td>8.9, NE</td>
</tr>
<tr>
<td>PBRM1 Gr. BAP1 WT &amp; PBRM1 MT</td>
<td>54</td>
<td>33.2</td>
<td>25.8, 45.0</td>
</tr>
<tr>
<td>WT Gr. BAP1 WT &amp; PBRM1 WT</td>
<td>37</td>
<td>33.1</td>
<td>15.5, 39.5</td>
</tr>
</tbody>
</table>

HR, 2.2; 95% CI, 1.1-4.3; P = 0.009
BAP1 and KDM5C Mutations: Mutual Exclusivity

BAP1 Group (19%)
BAP1 MT & PBRM1 WT/MT

PBRM1 Group (43%)
BAP1 WT & PBRM1 MT

WT Group (38%)
BAP1 WT & PBRM1 WT

BAP1
19%
PBRM1
46%
KDM5C
15%

BAP1 Gr (19%)
PBRM1 Gr (35%)
WT Gr (32%)
KDM5C Gr
(14%)

Genetic Alteration Missense Mutation Truncating Mutation

KDM5C as a Biomarker

Survival Probability
OS, months
Censored

KDM5C Mutant SUN-EVE
KDM5C Mutant EVE-SUN
KDM5C WT SUN-EVE
KDM5C WT EVE-SUN

Biomarker and Treatment Group
- KDM5C MT everolimus-sunitinib
- KDM5C WT everolimus-sunitinib
- KDM5C MT sunitinib-everolimus
- KDM5C WT sunitinib-everolimus

Number of patients at risk

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDM5C MT everolimus-sunitinib</td>
<td>11 8 7 6 5 0</td>
</tr>
<tr>
<td>KDM5C WT everolimus-sunitinib</td>
<td>21 20 16 12 8 1</td>
</tr>
<tr>
<td>KDM5C MT sunitinib-everolimus</td>
<td>98 74 49 42 26 0</td>
</tr>
<tr>
<td>KDM5C WT sunitinib-everolimus</td>
<td>90 69 51 45 20 2</td>
</tr>
</tbody>
</table>

p = 0.02

KDM5C as a Biomarker
Conclusions

• Specific tumor genotype might represent distinct molecular subtype of ccRCC with potentially predictive values for targeted therapies of different classes

• Tumor genotype might inform treatment sequence that impacts survival outcome

• Our analyses are retrospective and hypothesis generating that need further validation with independent datasets
Acknowledgments

The authors thank the patients, their families, and participating investigators.