Applying Advanced Genomics to Therapy Selection

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KCA 2015 Poll

• Is genomic data being used to guide decision-making at your institution?

Frequently (20%)
Rarely (52%)
Never (27%)

Courtesy of E. Jason Abel, MD (Presented at the 2015 Kidney Cancer Association Meeting, Miami, FL on November 6, 2015.)
Outline

Applying Advanced Genomics

Known Knowns

“There are things we know we know”

Known Unknowns

“We know there are some things we do not know”

Unknown Unknowns

“The ones we don’t know we don’t know”

Outline

Can genomics guide RCC therapy?

- **Known Knowns**
  - Genomic landscape of ccRCC and selected nccRCC
  - Prognostic role of selected genomic alterations

- **Known Unknowns**
  - Predictive role of selected genomic alterations

- **Unknown Unknowns**
  - Strategies for taking genomic profiling into the clinic
Can genomics guide RCC therapy?

Known Knowns
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Unknown Unknowns
- Strategies for taking genomic profiling into the clinic
Lessons from TCGA

- Widespread DNA hypomethylation associated with mutation of $SETD2$
- Aggressive cancers demonstrated metabolic shift
- PI3K/Akt pathway recurrently mutated
Genomic landscape of ccRCC and selected nccRCC

ROVER: Everolimus v GDC-0980 (N=85)

Genomic landscape of ccRCC and selected nccRCC

Lessons from TCGA

• 161 primary papillary RCC (PRCC) specimens
• Type I PRCC: Associated with \textit{MET} alterations
• Type II PRCC
  • Associated with \textit{NRF2-ARE}
  • \textit{CDKN2A} loss

Is MET relevant across all PRCC?

- 220 frozen from French RCC Network
- Copy number alterations (CNA) in:
  - 81% of type I PRCC (n=85)
  - 46% of type II PRCC (n=80)
- MET gene expression higher in type I and type II compared to normal tissue

Genomic landscape of ccRCC and selected nccRCC

Collecting duct RCC (n=17)

• **NF2** GAs could be associated with everolimus sensitivity
• **SMARCB1** GAs could be associated with EZH2 inhibitor sensitivity

Genomic landscape of ccRCC and selected nccRCC

Sarcomatoid RCC

- Increased AURKA-dependent activation of mTOR signaling in sarcomatoid RCC
- Could be targeted by available agents.

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Prognostic role of selected genomic alterations

PBRM1 and BAP1 in ccRCC (N=1,479)

Prognostic role of selected genomic alterations

16-Gene Recurrence Score (n=942 [CC], n=626 [France])

Prognostic role of selected genomic alterations

### Adjuvant trials

<table>
<thead>
<tr>
<th>Adjuvant Study</th>
<th>N</th>
<th>Agent</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 2805 (ASSURE)</td>
<td>1,865</td>
<td>Sunitinib/Sorafenib</td>
<td>Placebo</td>
</tr>
<tr>
<td>EVEREST</td>
<td>1,218</td>
<td>Everolimus</td>
<td>Placebo</td>
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<tr>
<td>S-TRAC</td>
<td>720</td>
<td>Sunitinib</td>
<td>Placebo</td>
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<tr>
<td>SORCE</td>
<td>1,656</td>
<td>Sorafenib</td>
<td>Placebo</td>
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<tr>
<td>PROTECT</td>
<td>1,500</td>
<td>Pazopanib</td>
<td>Placebo</td>
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<tr>
<td>ATLAS</td>
<td>592</td>
<td>Axitinib</td>
<td>Placebo</td>
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</tbody>
</table>

- No effective adjuvant treatment in 2015
- What are practical applications of prognostic markers?
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Predictive role of selected genomic alterations

**RECORD-3**

- Metastatic renal cell carcinoma
  - No prior systemic trx
  - Clear cell histology
  - Measurable disease
  - No organ dysfunction

- Vigorous effort to collect tissue; assessment with MSKCC IMPACT

Predictive role of selected genomic alterations

RECORD-3

Could $KDM5C$ predict outcome with VEGF-directed therapy?

Predictive role of selected genomic alterations

“Real world” use of genomic profiling

- 61 events of VEGF-directed therapy; long-term DOT in *KDM5C* MT

Predictive role of selected genomic alterations

Multi-Institutional Analysis of Everolimus Responders

<table>
<thead>
<tr>
<th>Mutation category</th>
<th>Mutations</th>
<th>Response Status</th>
<th>Fisher’s exact p-value*</th>
<th>Odds ratio (OR)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-Responder (n=36) n(%)</td>
<td>Responder (n=43) n(%)</td>
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<tr>
<td>MTOR, TSC1, TSC2</td>
<td>No (ref)</td>
<td>32(89)</td>
<td>31(72)</td>
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<tr>
<td></td>
<td>Yes</td>
<td>4(11)</td>
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<tr>
<td>MTOR, TSC1, TSC2, PTEN</td>
<td>No (ref)</td>
<td>27(75)</td>
<td>26(60)</td>
<td>0.13</td>
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<td></td>
<td>Yes</td>
<td>9(25)</td>
<td>17(40)</td>
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<tr>
<td>TSC1, TSC2</td>
<td>No (ref)</td>
<td>34(94)</td>
<td>34(79)</td>
<td>0.05</td>
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<td></td>
<td>Yes</td>
<td>2(6)</td>
<td>9(21)</td>
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<tr>
<td>TSC1, TSC2, MTOR, PTEN, PIK3CA</td>
<td>No (ref)</td>
<td>27(75)</td>
<td>25(58)</td>
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<tr>
<td></td>
<td>Yes</td>
<td>9(25)</td>
<td>18(42)</td>
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</tr>
</tbody>
</table>

- CR or PR or no tumor growth or any tumor shrinkage for at least 6 months

Predictive role of selected genomic alterations

Pembrolizumab in lung cancer

- PD-L1 does not work for nivo in RCC; what about mutational load?

Predictive role of selected genomic alterations

Nivolumab in renal cell carcinoma

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Strategies for taking genomic profiling into the clinic

S1500 (PI: Pal, Co-PIs: Shuch, Stein, Haas, Lara)

- **mPRCC**
  - Histologically confirmed diagnosis of PRCC
  - Measurable disease
  - 0-1 prior lines of therapy
  - No prior therapy with sunitinib
  - ECOG 0-1

- Randomization
  - Sunitinib
  - Cabozantinib
  - Crizotinib
  - Savolitinib

Primary Endpoint:
- Progression-free survival

Secondary Endpoints:
- Overall survival
- Response rate
- Adverse events

Exploratory evaluation of:
- MET mutational status
- MET expression

*Detailed analyses of:
- **MET** mutation
- **MET** amplification
Strategies for taking genomic profiling into the clinic

The previous dilemma in mRCC …
Strategies for taking genomic profiling into the clinic

The future dilemma in mRCC ...

Courtesy of Martin Voss, MD
Strategies for taking genomic profiling into the clinic

One possible idea …

Stratifcation by:
• Cytokine profile
• Mutational load, *KDM5C* mutation

Proposal from Tian Zhang, MD, Darren Feldman, MD, Toni Choueiri, MD, Monty Pal, MD and Daniel George, MD.
Strategies for taking genomic profiling into the clinic

Stool Bacteriomic Profiling of 20 Patients with mRCC receiving VEGF-TKI

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Rapid pace of discovery related to genomics of ccRCC and nccRCC

Need to focus on the next generation of genomically-driven clinical trials

Early understanding of how genomics may impact efficacy

Need to focus on the next generation of genomically-driven clinical trials
Acknowledgements

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  • Toni Choueiri, MD
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