Are the IMmotion151-molecular signatures predictive of treatment outcomes in the JAVELIN Renal 101 trial?

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1L Approved Combination Therapies in Advanced RCC

**IO-IO combination**

- Ipilimumab + Nivolumab
  - CheckMate-214

**IO-VEGF combinations**

- Pembrolizumab + Axitinib
  - KEYNOTE-426
- Nivolumab + Cabozantinib
  - Checkmate-9ER
- Avelumab + Axitinib
  - JAVELIN Renal 101
- Pembrolizumab + Lenvatinib
  - CLEAR

How to assign the right drug to the right patient?

Biomarker efforts in RCC

**IHC-IF**
- TCPDL1 + density of CD8⁺PD-1⁺TIM-3⁻LAG-3⁻ TIC associated with improved outcomes.

**Genomics**
- TMB not associated with response
- Loss of function of PBRM1, double-mutant in JR101.

**RNA**
- Angio, Teff, Myeloid
- Renal 101 Angio, Immuno
  - *IM151 molecular clusters*

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**Can we use molecular subtypes to choose the right therapy for each patient?**

2022 Kidney Cancer Research Summit

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Motzer R. et al., Cancer Cell 2020.
Motzer R. et al., JAMA Oncol 2022.
What are the IMmotion 151 molecular signatures?

<table>
<thead>
<tr>
<th>Molecular Cluster</th>
<th>HR (95%CI)</th>
<th>pvalue</th>
<th>Atezolizumab+Bevacizumab, mPFS</th>
<th>Sunitinib, mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Angio/stromal</td>
<td>1.11 (0.65-1.88)</td>
<td>0.708</td>
<td>15.3</td>
<td>13.9</td>
</tr>
<tr>
<td>2-Angiogenic</td>
<td>1.16 (0.82-1.63)</td>
<td>0.397</td>
<td>13.8</td>
<td>14.2</td>
</tr>
<tr>
<td>3-Complement</td>
<td>0.92 (0.63-1.34)</td>
<td>0.666</td>
<td>8.1</td>
<td>7.1</td>
</tr>
<tr>
<td>4-T-eff/Proliferative</td>
<td>0.52 (0.33-0.82)</td>
<td>0.005</td>
<td>10.9</td>
<td>6.1</td>
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<tr>
<td>5-Proliferative</td>
<td>0.47 (0.27-0.82)</td>
<td>0.007</td>
<td>8.3</td>
<td>4.3</td>
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<tr>
<td>6-Stromal/Proliferative</td>
<td>0.81 (0.52-1.25)</td>
<td>0.331</td>
<td>6.8</td>
<td>5.2</td>
</tr>
<tr>
<td>7-snoRNA</td>
<td>0.1 (0.01-0.77)</td>
<td>0.028</td>
<td>NR</td>
<td>7.4</td>
</tr>
<tr>
<td>Clusters 1 + 2</td>
<td>1.14 (0.86-1.52)</td>
<td>0.374</td>
<td>13.8</td>
<td>14</td>
</tr>
<tr>
<td>Clusters 4 + 5</td>
<td>0.52 (0.37-0.74)</td>
<td>2e-04</td>
<td>10.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Clusters 4 + 5 + 7</td>
<td>0.51 (0.36-0.71)</td>
<td>1e-04</td>
<td>12.4</td>
<td>5.6</td>
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HRs (95%CI) for mPFS
Do IMmotion 151 signatures help select the right treatment for the right patient?

Are these molecular markers predictive of outcomes in other treatment regimens?

NCT05361720 (planned)

Ipilimumab + Nivolumab IV every 21 days for 4 cycles.

Nivolumab IV on day 1 + Cabozantinib PO QD every 4 weeks.

Endpoints
- **Coprimary:** ORR
- **Secondary:** PFS, DOR, irAEs

1. Transcriptional (RNAseq)
2. Somatic alterations
3. PD-L1 IHC
4. Clinical risk
5. Clinical outcome
6. Sarcomatoid histology

**Molecular Subtype:**
- Angiogenic/Stromal
- Angiogenic
- Complement/ Oxidation
- T-effector/Proliferative
- Stromal/Proliferative
- SinoRNA

**Endpoints**
- Co-primary: ORR
- Secondary: PFS, DOR, irAEs

KCRS22
2022 Kidney Cancer Research Summit

#KCRS22 kcrs.kidneycon.org
Do molecular clusters predict benefit for an FDA-approved IO + VEGF regimen?

Random Forest Model

Training set IMmotion 151
Atezolizumab + Bevacizumab vs Sunitinib
not FDA-approved treatment

Validation set JAVELIN Renal 101
Avelumab + Axitinib vs Sunitinib
FDA-approved treatment
What do the IM151 clusters look like in the JR101 dataset?

Cluster 7 contains one patient per arm and is not represented on this slide.
Do the molecular clusters appear in the same proportions in a different dataset? Proportions of patients in each cluster and across IMDC groups are largely similar between both trials. Are they predictive of outcomes?
Do the molecular signatures predict response?

% of responders in IMmotion 151

- Angiogenic clusters favored response in the Sun arm
- Immune/Proliferative clusters favored response in the Atezo + Bev arm

% of responders in JAVELIN Renal 101

- Response rate was higher in the Axi + Avel arm regardless of molecular clusters

Response rates:
- P = 0.02*
- P = 0.004*
- P = 0.01*
- P = 0.01*
- N.S.
- N.S.
- P = 0.03*
- P = 0.0006**

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Do molecular clusters predict progression-free survival?

**IMmotion 151**

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<th>Sun mPFS</th>
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**JAVELIN RENAL 101**

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<th>Sun mPFS</th>
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<tr>
<td>1-Angio/stromal</td>
<td>0.55 (0.31-0.97)</td>
<td>0.037</td>
<td>15.1</td>
<td>7</td>
</tr>
<tr>
<td>2-Angiogenic</td>
<td>0.91 (0.61-1.35)</td>
<td>0.626</td>
<td>19.4</td>
<td>15.4</td>
</tr>
<tr>
<td>3-Complement</td>
<td>0.65 (0.43-0.97)</td>
<td>0.037</td>
<td>12.5</td>
<td>7.1</td>
</tr>
<tr>
<td>4-T-eff/Proliferative</td>
<td>0.54 (0.32-0.91)</td>
<td>0.02</td>
<td>20.6</td>
<td>6.9</td>
</tr>
<tr>
<td>5-Proliferative</td>
<td>0.83 (0.44-1.57)</td>
<td>0.562</td>
<td>5.7</td>
<td>8.4</td>
</tr>
<tr>
<td>6-Stromal/Proliferative</td>
<td>0.75 (0.44-1.26)</td>
<td>0.271</td>
<td>4.2</td>
<td>2.9</td>
</tr>
<tr>
<td>7-snoRNA</td>
<td>NA</td>
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Favors Atezo+Bev  ➞  Favors Sun
Favors Avel+Axi  ➞  Favors Sun

Axitinib + Avelumab combination yields improved PFS regardless of molecular clusters.
Conclusions and limitations

Are these molecular clusters real (i.e. same distribution)?
• Distribution of clusters in both trials is largely similar.

Are the IM151 signatures predictive of outcome for an FDA-approved treatment regimen?
• Axi+Avelumab, an FDA-approved combination improved outcomes regardless of molecular clusters.

Caveats
• The overlap of the profiled genes was not exactly the same between IM151 and JR101.
  • Do these conclusions apply to other regimens?
The JR101 study is an ongoing trial (NCT02684006) sponsored by Pfizer and is part of an alliance between Pfizer and the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Patients and their families

Pfizer team