Bridging Academia and Industry Through Biomarker Work in RCC

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Pfizer
DISCLOSURE

• I am an employee of Pfizer.
Outline

• Intro- about me

• Research in academia vs industry

• All biomarkers are not created equal

• Industry/academic cooperation

• Summary/Conclusion
Research is Research

Science Online Apr. 12, 2013, Opening industry-academic partnerships Chris Tachibana

Research in academia vs industry

Research is research
- Primary goals aligned: to help patients and advance the field
- Research/publication considerations differ (QC, regulatory, legal, business)
- A key difference is often the scale at which biological questions can be examined

Complex and/or rare markers, patterns or interrelationships require large data sets for identification and validation
- Academia has cutting edge tools, expertise and resources not available in industry
- Industry sponsors have the ability to generate data sets powered to identify clinically and biologically meaningful attributes

We have a responsibility to maximize the value of samples and data collected from patients who participate in our trials
Patient Enrichment Biomarkers Improve Success Rates


- Biomarker-driven patient selection for early clinical trials, Rodrigo Dienstmann, Jordi Rodon, and Josep Tabernero,
- Curr Opin Oncol 2013, 25:305–312

Table 1. Response rate of successful targeted therapies in molecularly-selected populations evaluated in early clinical trials

<table>
<thead>
<tr>
<th>Marker/patient population</th>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 overexpressed/amplified breast cancer</td>
<td>Trastuzumab</td>
<td>anti-HER2 antibody</td>
<td>12%</td>
<td>[6]</td>
</tr>
<tr>
<td>CD117 overexpressed GIST</td>
<td>Imatinib</td>
<td>c-KIT, PDGF inhibitor</td>
<td>44%</td>
<td>[12]</td>
</tr>
<tr>
<td>BRCA1/2 mutant breast, ovarian and prostate cancer</td>
<td>Olaparib</td>
<td>PARP inhibitor</td>
<td>54%</td>
<td>[13]</td>
</tr>
<tr>
<td>BRAF V600E mutant melanoma</td>
<td>Venetoclax</td>
<td>BRAF inhibitor</td>
<td>75%</td>
<td>[8]</td>
</tr>
<tr>
<td>Basal cell carcinomas (majority have inactivating mutations in PTCH1 or activation of SMO)</td>
<td>Vemurafenib</td>
<td>BRAF inhibitor</td>
<td>60%</td>
<td>[14]</td>
</tr>
<tr>
<td>AUF rearranged NSCLC</td>
<td>Crizotinib</td>
<td>AUR, MET inhibitor</td>
<td>58%</td>
<td>[15]</td>
</tr>
<tr>
<td>Medullary thyroid cancer (known to have RET mutations, MET expression and VEGF activation)</td>
<td>Cabozantinib</td>
<td>MET, VEGFR2, RET inhibitor</td>
<td>57%</td>
<td>[16]</td>
</tr>
<tr>
<td>PECMA mutant breast cancer</td>
<td>BY719</td>
<td>selective PD3, alpha inhibitor</td>
<td>44%*</td>
<td>[10]</td>
</tr>
<tr>
<td>FGFR1 or FGFR amplified breast cancer</td>
<td>E3810</td>
<td>FGFR, VEGFR</td>
<td>70%</td>
<td>[11]</td>
</tr>
</tbody>
</table>

* Tumor shrinkage > 20%
Distance traveled to site as a predictor of OS

Elucidating the Determinants of Response:
Elucidating the Determinants of Response:

Germline mutations
- MMR deficiency
- POLE mutations
- BRCA1/2 mutations

Genomic Instability, Mutational load

IFN/JAK/STAT signaling
- JAK 1/2 mutations
- JAK3 activating mutation
- Chronic IFN-γ exposure

Epigenetic changes
- DNMT, EZH2 inhibition

Somatic mutations
- Wnt/ß-catenin activation
- PTEN loss

Transcriptional programs
- IPRE5 signature
- Tumor aneuploidy

APCs/DCs
- Class II MHC
- MHC I downregulation
- Neoantigen load
- B2M mutations

Promotes resistance to ICI

Promotes sensitivity to ICI

T-cell exhaustion

CD8+ T effector/memory cells
- Cytolytic activity (GZMA, PRF1)

Th1 cells
- Th1 cytokines (CXCL9, CXCL10)

MDSCs
- Peptide inhibition

Tregs


#KCRS19

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Biomarker analyses from JAVELIN Renal 101: avelumab + axitinib vs sunitinib in advanced renal cell carcinoma


1The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA; 2Institut Gustave Roussy, Villejuif, France; 3Netherlands Cancer Institute, Amsterdam, the Netherlands; 4The Royal Marsden NHS Foundation Trust, London, United Kingdom; 5Osaka University Hospital, Osaka, Japan; 6City of Hope Comprehensive Cancer Center, Duarte, CA, USA; 7Institut Paoli-Calmettes, Marseille, France; 8The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 9Private Medical Institution “Euromedservice,” St Petersburg, Pushkin, Russian Federation; 10University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; 11Pfizer Inc, San Diego, CA, USA; 12Pfizer Inc, Cambridge, MA, USA; 13Pfizer SRL, Lombardia, Italy; 14Memorial Sloan Kettering Cancer Center, New York, NY, USA
Introduction

• In the JAVELIN Renal 101 study, the combination of avelumab + axitinib showed a longer PFS and a higher ORR than sunitinib as first-line treatment for patients with advanced RCC\(^1\)

• Analyses of baseline tumor samples were undertaken to provide insight into potential predictive biomarkers
**JAVELIN Renal 101: study design**

### Key eligibility criteria
- Treatment-naive advanced RCC with a clear cell component
- ≥ 1 measurable lesion as defined by RECIST v1.1
- Tumor tissue available for PD-L1 staining
- ECOG PS 0 or 1

### Stratification
- ECOG PS (0 vs 1)
- Geographic region (USA vs Canada/Western Europe vs ROW)

### Treatment regimens
- **Sunitinib 50 mg PO QD** (4 weeks on, 2 weeks off)
- **Avelumab 10 mg/kg IV Q2W** + Axitinib 5 mg PO BID (6-week cycle)

### Primary objective
To demonstrate the superiority of avelumab + axitinib compared with sunitinib for either PFS or OS in patients with PD-L1+ tumors
Progression-Free Survival in the PD-L1–Positive Group (A) and the Overall Population (B)

## JAVELIN Renal 101: efficacy summary¹⁻³

<table>
<thead>
<tr>
<th>PD-L1+ group (N = 560)</th>
<th>Overall population (N = 886)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avelumab + axitinib (N = 270)</td>
</tr>
<tr>
<td><strong>PFS per IRC</strong></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>13.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>11.1, NE</td>
</tr>
<tr>
<td>Benefit vs sunitinib (HR; 2-sided P value)</td>
<td>0.61; P = 0.0001</td>
</tr>
<tr>
<td><strong>ORR per IRC, %</strong></td>
<td>55.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>49.0, 61.2</td>
</tr>
<tr>
<td><strong>PFS per investigator assessment</strong></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>13.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>9.8, NE</td>
</tr>
<tr>
<td>Benefit vs sunitinib (HR; 2-sided P value)</td>
<td>0.51; P &lt; 0.0001</td>
</tr>
<tr>
<td><strong>ORR per investigator assessment, %</strong></td>
<td>61.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>55.8, 67.7</td>
</tr>
</tbody>
</table>

IRC, independent review committee; NE, not estimable; ORR, objective response rate, PFS, progression-free survival.

Data cutoff date: June 20, 2018; median follow-up, 12.0 months (avelumab + axitinib) and 11.5 months (sunitinib).

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Assay</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 expression n=804</td>
<td>• IHC: Ventana SP263</td>
<td>• ≥1% PD-L1+ IC for IHC (+ vs −)</td>
</tr>
<tr>
<td>CD8 expression n=795</td>
<td>• IHC: clone C8/144B</td>
<td>• Median value (≥ vs &lt;)</td>
</tr>
<tr>
<td>Gene expression profiling n=720</td>
<td>• RNA-seq: Illumina NovaSeq</td>
<td>• Median value (≥ vs &lt;)</td>
</tr>
<tr>
<td>Mutations and polymorphisms n=733</td>
<td>• Whole-exome sequencing: Illumina NovaSeq</td>
<td>• Presence of protein-altering somatic mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Polymorphisms in Fcγ receptor genes that alter the affinity for IgG1</td>
</tr>
</tbody>
</table>

All analyses were performed on baseline tumor biopsies collected within 1 year of screening and prior to systemic therapy.

IC, immune cell; IHC, immunohistochemistry; RNA-seq, RNA sequencing.
Derivation of the 26-gene JAVELIN Renal 101 signature

- Whole transcriptomic data from 720 baseline tumor samples (350 in the avelumab + axitinib arm, 370 in the sunitinib arm) were filtered for informative genes
  - Genes with low or invariant expression were removed
  - 4,622 genes remained after initial filtering

- Blinded to clinical outcome, co-expression analysis identified a module of 306 genes

- High expression of a 306-gene signature was associated with better PFS in the avelumab + axitinib arm but not in the sunitinib arm

- Further filtering of the co-expressed 306 genes based on immune-related functionality and most significant association with PFS in the avelumab + axitinib arm identified a 26-gene subset

* Genes included in > 1 functional group

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**Functional Groups and Genes**

- **T-cell receptor signaling**
  - CD3G, CD3E, CD8B, THEMIS, TRAT1, GRAP2, CD247

- **T-cell activation, proliferation, and differentiation**
  - CD2,* CD96,* PRF1,* CD6, IL7R, ITK, GPR18, EOMES, SIT1, NLRC3

- **NK cell–mediated cytotoxicity**
  - CD2,* CD96,* PRF1,* CD244, KLRD1, SH2D1A

- **Chemokine**
  - CCL5, XCL2

- **Other immune response genes**
  - CST7, GFI1, KCNA3, PSTPIP1

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* Genes included in > 1 functional group
PFS according to 26-gene JAVELIN Renal 101 signature

**Avelumab + axitinib**

- **Median PFS (95% CI), mo**
  - ≥ Median value: 15.2 (12.5, NE)
  - < Median value: 9.8 (8.6, 12.2)

- Unstratified HR (≥ Median vs < Median), 0.60 (95% CI: 0.439, 0.834); 2-sided P = 0.0019

**Sunitinib**

- **Median PFS (95% CI), mo**
  - ≥ Median value: 8.3 (7.0, 11.1)
  - < Median value: 9.0 (7.1, 9.8)

- Unstratified HR (≥ Median vs < Median), 0.89 (95% CI: 0.670, 1.172); 2-sided P = 0.3973

**Progression-free survival, %**

- No. at risk
  - ≥ Median
    - Avelumab + axitinib: 170
    - Sunitinib: 191
  - < Median
    - Avelumab + axitinib: 180
    - Sunitinib: 179

**Months**

- No. at risk
  - ≥ Median
    - Avelumab + axitinib: 136
    - Sunitinib: 115
  - < Median
    - Avelumab + axitinib: 60
    - Sunitinib: 43

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NE, not estimable; PFS, progression-free survival.
Verification of the 26-gene JAVELIN Renal 101 signature in an independent data set

The 26-gene JAVELIN Renal 101 signature also enriched for responders to avelumab + axitinib when tested in an independent data set derived from the single-arm, phase 1b JAVELIN Renal 100 clinical trial¹

<table>
<thead>
<tr>
<th>Avelumab + axitinib</th>
<th>Median PFS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Median value</td>
<td>NE (5.3, NE)</td>
</tr>
<tr>
<td>&lt; Median value</td>
<td>5.7 (2.9, 11.1)</td>
</tr>
</tbody>
</table>

Unstratified HR (≥ Median vs < Median), 0.36 (95% CI: 0.157, 0.805); 2-sided P = 0.0097

Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial

PFS according to mutations and polymorphisms

<table>
<thead>
<tr>
<th>Gene</th>
<th>Log₂ HR (95% CI)</th>
<th>HR (95% CI)*</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAP1</td>
<td>Mutant vs Wild type</td>
<td>0.69 (0.43, 1.09)</td>
<td>1.33 (0.93, 1.90)</td>
</tr>
<tr>
<td>CD163L1</td>
<td>0.20 (0.05, 0.80)</td>
<td>1.71 (1.01, 2.92)</td>
<td>0.0114</td>
</tr>
<tr>
<td>DNMT1</td>
<td>0.34 (0.12, 0.91)</td>
<td>1.66 (0.96, 2.87)</td>
<td>0.0245</td>
</tr>
<tr>
<td>IL6</td>
<td>0.54 (0.35, 0.85)</td>
<td>1.10 (0.78, 1.56)</td>
<td>0.0071</td>
</tr>
<tr>
<td>MC1R</td>
<td>0.25 (0.08, 0.79)</td>
<td>1.19 (0.58, 2.42)</td>
<td>0.0109</td>
</tr>
<tr>
<td>PTEN</td>
<td>2.30 (1.46, 3.64)</td>
<td>1.27 (0.84, 1.91)</td>
<td>0.0002</td>
</tr>
<tr>
<td>VHL</td>
<td>0.92 (0.67, 1.27)</td>
<td>1.11 (0.84, 1.46)</td>
<td>0.6048</td>
</tr>
<tr>
<td>SNP</td>
<td>FCGR2A</td>
<td>0.95 (0.68, 1.33)</td>
<td>0.97 (0.72, 1.31)</td>
</tr>
<tr>
<td></td>
<td>1.05 (0.76, 1.46)</td>
<td>1.52 (1.15, 2.01)</td>
<td>0.7469</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; SNP, single nucleotide polymorphism.
* Cox proportional hazards model with Wild type as the reference group was used to calculate HR and 95% CI. An HR < 1 indicates better survival in the Mutant group, while an HR > 1 indicates better survival in the Wild type group.
† Log-rank 2-sided test was performed to compare between Wild type/Mutant groups.
PFS according to genotype

**CD163L1** | scavenger receptor
---|---
Avelumab + axitinib | Median PFS (95% CI), mo
Mutant | 11.1 (9.5, NE)
Wild type | 12.2 (9.8, 14.1)

**DNMT1** | DNA methyltransferase
---|---
Avelumab + axitinib | Median PFS (95% CI), mo
Mutant | 7.0 (5.5, 9.9)
Wild type | 13.0 (11.5, 16.1)

**PTEN** | tumor suppressor
---|---
Avelumab + axitinib | Median PFS (95% CI), mo
Mutant | 1.45 (1.19, 1.70)
Wild type | 3.64 (3.17, 4.10)

Mut, mutant; NE, not estimable; PFS, progression-free survival; WT, wild type.
Summary

• The novel JAVELIN Renal 101 signature comprised immune-related genes most significantly associated with PFS in the avelumab + axitinib arm and was verified in an independent data set (single-arm, phase 1b JAVELIN Renal 100 trial of avelumab + axitinib\(^1\))

• Significant treatment arm–specific differences in PFS were observed relative to wild type when mutations in genes such as \(CD163L1\), \(DNMT1\), or \(PTEN\) were present

• These findings define molecular features that differentiate therapy-specific outcomes with I-O + TKI in first-line advanced RCC and may inform personalized therapy strategies for patients with advanced RCC

• Examination of blood-based biomarkers in serial samples as well as further investigation of the relevance and significance of these findings is ongoing

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Conclusion

• We have a responsibility to maximize the value of samples/data collected from patients who participate in our trials

• The identification and development of meaningful biomarkers requires significant investments to collect and analyze patient samples and data from well designed, adequately powered, randomized studies

• Our best opportunity to help patients and advance the field is to expand industry/academic cooperation to take advantage of the combined strengths and resources of each institution
Acknowledgments

• We thank the patients and their families, investigators, co-investigators, and study teams at each of the participating centers and at Pfizer Inc

• This trial was sponsored by Pfizer Inc and is part of an alliance between Pfizer Inc and Merck KGaA, Darmstadt, Germany
Thank you for your attention