Vaccines for RCC:
Rationale and Clinical Update

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Disclosure

Research Funding:
Pfizer, BMS, Newlink Genetics

Honoraria: BMS
Outline

- Rationale for a Cancer Vaccine

- Vaccines for RCC:
  - IMX-9001: A peptide-based vaccine
  - AGS-003: A DC-based autologous vaccine

- Newlink Hyperacute Renal, a novel vaccine construct
Combined Checkpoint Blockade: I.e. Do We Really Even NEED a Vaccine?

- Primary endpoint: Safety (AEs, laboratory tests)
- Secondary endpoint: Efficacy (ORR, duration of response, PFS)
- Exploratory endpoint: Response by tumor PD-L1 status
- Study assessments: Tumor response (RECIST v1.1) evaluated at screening, every 6 weeks (first 4 assessments), then every 12 weeks until disease progression

ORR, objective response rate.
TKI cohort presented by Amin A et al. ASCO 2014, Abstract 5010

Hans Hammers at 2014 ASCO Annual Meeting
Response Rate = Good
(But not 90-100%)

N3 + I1 (n=20)

N1 + I3 (n=22)

Positive change in tumor burden indicates tumor growth; negative change indicates tumor reduction.
## Toxicity: Significant

<table>
<thead>
<tr>
<th>Event</th>
<th>All</th>
<th>Grade 3-4</th>
<th>All</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with an event, n (%)</td>
<td>16 (76.2)</td>
<td>6 (28.6)</td>
<td>23 (100)</td>
<td>14 (60.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (52.4)</td>
<td>0</td>
<td>16 (69.6)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (38.1)</td>
<td>0</td>
<td>4 (17.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (28.6)</td>
<td>0</td>
<td>5 (21.7)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (28.6)</td>
<td>1 (4.8)</td>
<td>8 (34.8)</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>4 (19.0)</td>
<td>0</td>
<td>3 (13.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (19.0)</td>
<td>0</td>
<td>9 (39.1)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (19.0)</td>
<td>0</td>
<td>4 (17.4)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (14.3)</td>
<td>0</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (14.3)</td>
<td>0</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3 (14.3)</td>
<td>0</td>
<td>6 (26.1)</td>
<td>0</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>3 (14.3)</td>
<td>3 (14.3)</td>
<td>6 (25.1)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
<td>3 (13.0)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1 (4.8)</td>
<td>0</td>
<td>9 (39.1)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>0</td>
<td>9 (39.1)</td>
<td>3 (13.0)</td>
</tr>
</tbody>
</table>

- No grade 5 treatment-related AEs were reported.

Presented By Hans Hammers at 2014 ASCO Annual Meeting
Cancer Vaccine Goal ….  
Dendritic Cells Traffic and Present Antigen To Specific CD4 and CD8 T Cells in the Draining Lymph node  
(i.e. turn a non-inflammed tumor inflammed)
Using Autologous RNA to Load Dendritic Cells: Argos AGS-003

1. Kidney Cancer Sample
2. Leukapheresis Product
3. Tumor RNA Isolation
4. DC Manufacture
5. Load DC With RNA And Activate (AGS-003)
6. Cryopreserve
7. Intranodal Injection

Diagram:
- Kidney Cancer Sample
- Leukapheresis Product
- Tumor RNA Isolation
- DC Manufacture
- Load DC With RNA And Activate (AGS-003)
- Cryopreserve
- Intranodal Injection
**ADAPT:**

**Autologous Dendritic Cell Immunotherapy with AGS-003 Plus Sunitinib for the Treatment of Advanced RCC**

- **Primary end point:** OS (30% increase)
- **Secondary end point:** ORR, PFS, Safety

**Randomize**

1. **Metastatic, unfavorable risk clear cell RCC**
2. **N= 600**

**1 Cycle Sutent (6 wks)**
- **AGS-003**
  - 5 doses Q 3 wks
  - AGS-003 Q 3 months
- **Placebo**
  - 5 doses Q 3 wks
  - Placebo Q 3 months

**Ongoing Sutent (4 wks on, 2 wks off)**
Protein + Adjuvant (the traditional vaccine)

CEA
Her2Neu
Mart1

"Vaccine"
A Better Vaccine: Chose Better Antigens (Immatics)
And The TUMAP’s Are ......

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Antigen</th>
<th>HLA</th>
<th>Overexpression</th>
<th>In vitro immunogenicity</th>
<th>Remarks on function and tumor relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADF-001 (SVASTITGV)</td>
<td>PLIN2</td>
<td>A*02</td>
<td>6.0</td>
<td>+</td>
<td>Major constituent of the surface of lipid droplets. Overexpressed in several cancers; established as a marker for RCC.</td>
</tr>
<tr>
<td>ADF-002 (VMAGDIYSV)</td>
<td>APOL1</td>
<td>A*02</td>
<td>6.0</td>
<td>+</td>
<td>Secreted major apoprotein of high-density lipoprotein. Overexpression in RCC.</td>
</tr>
<tr>
<td>APO-001 (ALADGVQKV)</td>
<td></td>
<td>A*02</td>
<td>7.0</td>
<td>+</td>
<td>Cell cycle regulation. Overexpression and association with tumorigenesis and metastasis described for various tumors.</td>
</tr>
<tr>
<td>CCN-001 (LLGATCMFV)</td>
<td>CCND1</td>
<td>A*02</td>
<td>3.0</td>
<td>+</td>
<td>cGMP synthesis. Proangiogenic effects in tumors.</td>
</tr>
<tr>
<td>GUC-001 (SVFAGVGVG)</td>
<td>GUCY1A3</td>
<td>A*02</td>
<td>2.2</td>
<td>+</td>
<td>Largely uncharacterized so far. Overexpression in RCC.</td>
</tr>
<tr>
<td>K67-001 (ALFDGDPHL)</td>
<td>PRUNE2</td>
<td>A*02</td>
<td>3.4</td>
<td>+</td>
<td>Hepatocyte growth factor receptor tyrosine kinase, cell signaling. Various implications in malignant transformation and invasiveness of tumor cells.</td>
</tr>
<tr>
<td>MET-001 (YVDPVITSI)</td>
<td>MET</td>
<td>A*02</td>
<td>13.6</td>
<td>+</td>
<td>Protection against pathogen binding to the cell surface; roles in cell signaling. Altered glycosylation patterns lead to new T cell epitopes in tumors.</td>
</tr>
<tr>
<td>MUC-001 (STAPPVHNV)</td>
<td>MUC1</td>
<td>A*02</td>
<td>1.6</td>
<td>+</td>
<td>Regulation of cell signaling. Overexpression during neovascularization in tumors.</td>
</tr>
<tr>
<td>RGS-001 (LAALPHSCL)</td>
<td>RGS5</td>
<td>A*02</td>
<td>3.5</td>
<td>+</td>
<td>Breakdown of extracellular matrix during tissue remodeling. Involved in tumor invasion and metastasis, tumor development and progression. Also, roles in apoptosis, cell proliferation and cell differentiation.</td>
</tr>
<tr>
<td>MMP-001 (SQDDIKGIGKLYGKR)</td>
<td>MMP7</td>
<td>DR</td>
<td>3.3</td>
<td>+</td>
<td>Marker peptide, not tumor associated. HBCAg is an antigenic determinant of HBV. Serological responses develop in most HBV-infected subjects, used for diagnosis of infection.</td>
</tr>
</tbody>
</table>
IMA901 Renal Cell Cancer Phase 3 trial
IMA901-301 study

Stratification:
• Risk group (low vs intermediate)
• Region (WEE vs. CEE vs. US vs. Asia)
• Nephrectomy (yes vs. no)

Follow-up for PFS
Every 12 weeks
Max. 19 months

Vaccination Phase 4 months
10 IMA901/GM-CSF vaccinations

Primary endpoint
• Overall Survival

Secondary endpoints
• Overall Survival in biomarker-defined subgroup (pre-specified)
• Progression-free survival (PFS)
• Safety and tolerability
• Cellular immunomonitoring

IMA901 plus GM-CSF (i.d.)

Sunitinib

Sunitinib until progression or toxicity

- Sunitinib (1 cycle)
- R 3:2

Cyclophosphamide
(300 mg/m² as single infusion)

IMA091 is a vaccine comprised of multiple, RCC tumor-associated peptides

N=330
• 1st line metastatic and/or locally advanced RCC
• HLA-A*02-positive
• Documented tumor lesions
• Favorable or intermediate risk (Heng et al., 2009)
HYPERACUTE RENAL consists of tumor-specific human cancer cell lines genetically altered to express a unique carbohydrate, $\alpha$-gal.

Humans have pre-existing immune response to $\alpha$-gal.

HYPERACUTE RENAL is an allogeneic whole-cell vaccine that utilizes this potent, pre-existing immune response against $\alpha$-gal to educate the immune system and attack cancer.
Proposed Mechanism

Pre-Existing “HyperAcute” Anti-αGal Antibody Response

1. Pre-existing hyperacute anti-αGal antibody response leads to...

2. Cellular infiltration
   - APCs, NK, NK-T cells
   - Eosinophilia, anti-Parasitic-Like response

3. Humoral Immunity:
   - Anti-Tumor Antibodies

4. Cellular Immunity:
   - Tumor-specific T cells
# Alpha-Gal HYPERACUTE RENAL

**Potential Critical Success Factors**

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## Formulation

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>✓</td>
<td>Metabolically Active live Whole Cell Vaccine</td>
</tr>
<tr>
<td>✓</td>
<td>Expression of Polyvalent tumor antigens</td>
</tr>
<tr>
<td>✓</td>
<td>Presence of tumor antigens shared with Patient’s cancer</td>
</tr>
<tr>
<td>✓</td>
<td>Not patient specific, adaptable logistics and manufacture</td>
</tr>
</tbody>
</table>

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## Mechanism of Action

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>✓</td>
<td>Relies on pre-existing antibody response</td>
</tr>
<tr>
<td>✓</td>
<td>Complement mediated destruction of vaccine cells, immune-activation &amp; cross-presentation of tumor antigens</td>
</tr>
<tr>
<td>✓</td>
<td>Tumor specific CD8+ cytotoxic T cells are generated to recognize patient’s own tumor</td>
</tr>
<tr>
<td>✓</td>
<td>Tumor specific immune response recognizing shared tumor antigens is generated post vaccination</td>
</tr>
</tbody>
</table>
Adaptive Immune Resistance:

(If the Vaccine Induces a Good T Cell Response: The T cells Will Express PD-1 AND The tumor will defend itself by up-regulating PD-L1)

Drake CG and Pardoll D, JEM 2011
Adaptive Immune Resistance: Synergism Between Vaccination and PD-1 Blockade

Jooss et. al, *Cancer Res*, 2010
Summary

- Checkpoint Blockade in RCC = Outstanding Clinical Promise
  - Not 100% RR
  - Some toxicity with combined checkpoint blockade

- Vaccines: Prime a Previously Unrecognized (or poorly recognized) Tumor
  - ARGOS DC Vaccine (in Phase III)
  - Immatics Peptide Vaccine (in Phase III)

- Alpha-Gal Based Vaccine – Novel Vaccine Strategy
  - Phase I Open (JHU, UIOWA)

- Adaptive Immune Resistance and the potential for synergy with Immune Checkpoint Inhibitors