Renal function before and after cytoreductive nephrectomy in a phase 3 randomized clinical trial

Presenting author: Erik N. Mayer
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• I do not intend to discuss an unapproved use of a commercial product/device in my presentation.
Background

- Cytoreductive nephrectomy (CN) + immunotherapy = improvement in overall survival (OS) for patients with mRCC

- Renal function before and after surgery in patients undergoing CN is poorly understood in patients with advanced kidney cancer

- ADAPT (The Autologous Dendritic Cell Immunotherapy (AGS-003) Plus Standard Treatment of Advanced Renal Cell Carcinoma)
**ADAPT Phase 3 Trial**

### Pre-treatment
- Diagnosis, Nephrectomy, Screening

### Randomization
- 2 : 1
- ↓
- Leukapheresis
  - (Treatment group only)

### Induction
- Treatment group: AGS-003 + Sunitinib/Standard Therapy†
- Control group: Sunitinib/Standard Therapy†

- **Sunitinib**
  - 6 week cycle

- **AGS-003**
  - 8 doses over 48 weeks

- **Standard therapy†**
  - over 48 weeks

- ≥SD

- **Continued Standard therapy† until PD**

### Booster
- **Sunitinib**
  - 6 week cycle

- **AGS-003**
  - quarterly until PD

- **Standard therapy†**
  - until PD

- ≥SD

†Standard therapy initiates with 6-week cycles of sunitinib (50 mg daily for 4 weeks, 2 weeks rest). Other compatible agents may be substituted for sunitinib due to PD prior to week 48 restaging, or due to intolerance at any time for patients continuing to benefit.
Product production requires only a minute tumor specimen, allowing treatment of earlier stage as well as later stage cancer patients.

A single production run makes enough product to continuously treat the patient for several years.
Objective

• Assess renal function before and after CN in patients with mRCC participating in ADAPT trial
Methods

- Retrospective review of prospectively collected data on tumor characteristics, established chronic kidney disease (CKD) risk factors, and patient socio-demographics
- Univariate and multivariate logistic regression analysis to evaluate impact of patients and disease specific risk factors on pre-operative renal function.
- Report post-operative change in GFR
### Renal Function Staging

- **National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF - KDOQI)**

**KDOQI-defined Stages of CKD**

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR$^\text{II}$ (mL/min)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90+</td>
<td>Kidney damage with normal or increased GFR</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>Kidney damage with mild decrease in GFR</td>
</tr>
<tr>
<td>3</td>
<td>30–59</td>
<td>Moderate decrease in GFR</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>Severe decrease in GFR</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or on dialysis</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>
Results

• 1007 patients at 113 centers worldwide with pre-operative kidney function data (CN or partial)

• 426 patients with post-operative kidney function data

• 198 (19.7%) patients had stage 3 or greater CKD (GFR < 60ml/min/1.73 m²) at baseline
• Exclusion/Inclusion criteria for pre-operative analysis

Initial File (2013-July 2015 patients w/ surgical data)
- 1148
- 1092 CN
- 957
- 717
- 240 missing at least one risk factor variable
- 135 missing pre-op creatinine lab
- 50 partial 6 missing
<table>
<thead>
<tr>
<th>Independent Variable (reference category)</th>
<th>Univariate OR (95% CI)</th>
<th>p-value</th>
<th>Multivariate OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.062 (1.041-1.083)</td>
<td>&lt;.0001</td>
<td>1.064 (1.042-1.087)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.907 (0.599-1.372)</td>
<td>0.643</td>
<td>0.805 (0.518-1.252)</td>
<td>0.3483</td>
</tr>
<tr>
<td>Race (White)</td>
<td>1.413 (0.484-14.295)</td>
<td>&lt;0.001</td>
<td>2.704 (0.488-14.967)</td>
<td>0.2547</td>
</tr>
<tr>
<td>Asian</td>
<td>0.499 (0.104-2.358)</td>
<td>0.356</td>
<td>0.505 (0.107-2.379)</td>
<td>0.388</td>
</tr>
<tr>
<td>Black</td>
<td>&lt;0.001 (&lt;0.001-&gt;999.999)</td>
<td>0.985</td>
<td>&lt;0.001 (&lt;.001-&gt;999.99)</td>
<td>0.9841</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>6.360 (1.052-38.457)</td>
<td>0.044</td>
<td>7.251 (&lt;.001-&gt;999.99)</td>
<td>0.679</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical Approach (laparoscopic)</td>
<td>1.026 (0.696-1.512)</td>
<td>0.897</td>
<td>0.998 (0.654-1.525)</td>
<td>0.9936</td>
</tr>
<tr>
<td>T classification (T3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0.465 (0.216-1.001)</td>
<td>0.050</td>
<td>0.432 (0.192-0.969)</td>
<td>0.0418</td>
</tr>
<tr>
<td>T2</td>
<td>0.253 (0.100-0.643)</td>
<td>0.004</td>
<td>0.303 (0.117-0.788)</td>
<td>0.0143</td>
</tr>
<tr>
<td>T4</td>
<td>0.887 (0.430-1.829)</td>
<td>0.746</td>
<td>0.965 (0.45-2.073)</td>
<td>0.9277</td>
</tr>
<tr>
<td>Clinical stage ≥ 3</td>
<td>2.953 (1.617-5.394)</td>
<td>&lt;.0001</td>
<td>2.871 (1.528-5.395)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Albumin &lt; LLN</td>
<td>0.870 (0.543-1.393)</td>
<td>0.561</td>
<td>0.767 (0.464-1.266)</td>
<td>0.2992</td>
</tr>
<tr>
<td>LDH &gt; ULN</td>
<td>1.705 (1.166-2.493)</td>
<td>0.006</td>
<td>1.851 (1.231-2.781)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Symptoms of Metastasis</td>
<td>0.677 (0.458-1.000)</td>
<td>0.050</td>
<td>0.714 (0.472-1.081)</td>
<td>0.1111</td>
</tr>
<tr>
<td>Retroperitoneal Adenopathy</td>
<td>1.045 (0.710-1.538)</td>
<td>0.825</td>
<td>1.062 (0.693-1.628)</td>
<td>0.7809</td>
</tr>
<tr>
<td>Supradiaphragmatic Adenopathy</td>
<td>0.844 (0.543-1.312)</td>
<td>0.450</td>
<td>0.821 (0.505-1.333)</td>
<td>0.4243</td>
</tr>
</tbody>
</table>
Factors associated with pre-op stage 3 or greater CKD on multivariate analysis:

- **Age** (OR: 1.064, 95% CI: 1.042-1.087, p<.0001)
- **LDH > ULN** (OR: 1.851, 95% CI: 1.231-2.781, p=0.002)
- **Clinical stage ≥ 3** (OR: 2.871, 95% CI: 1.528-5.395, p=0.001)
Results

• The likelihood of having ≥ stage 3 CKD at surgery was lower for T1 (OR 0.432, 95% CI: 0.192-0.969, p<0.042) and T2 disease (OR: 0.303, 95% CI: 0.117-0.788, p<0.014) than for T3, but T3 v. T4 were not different (p=0.9277).

• Gender, race, low albumin, symptoms of metastasis, and adenopathy were NOT significantly associated with pre-operative CKD stage 3 or greater.
Selection Criteria

- Exclusion/Inclusion criteria for post-operative analysis

- Cytoreductive Nephrectomy
  - Initial File (2013-July 2015 patients w/ surgical data) 1148
  - 1092 CN
  - 50 partial 6 missing

- Randomized to trial (Pre- and post-op creatinine)
  - 426
  - 666 missing pre- or post-op creatinine
Median time from CN to post-op GFR lab value: 34 days

Median ΔGFR after CN: -21.6 ml/min/1.73 m²

27.6% average decrease in renal function after CN
• 160 (37.6%) patients developed CKD ≥ 3 post-CN

• 14 (3.3%) improved to CKD ≤ 3 post-CN

<table>
<thead>
<tr>
<th>Pre-operative CKD Stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count (Total %) (Row %)</td>
<td>20 (4.7%) (12.9%)</td>
<td>100 (23.5%) (64.5%)</td>
<td>35 (8.2%)</td>
<td>0</td>
<td>155 (36.4%)</td>
</tr>
<tr>
<td>II Count (Total %) (Row %)</td>
<td>3 (0.7%) (1.5%)</td>
<td>71 (16.7%) (35.7%)</td>
<td>122 (28.6%) (61.3%)</td>
<td>3 (0.7%)</td>
<td>199 (46.7%)</td>
</tr>
<tr>
<td>III Count (Total %) (Row %)</td>
<td>0</td>
<td>14 (3.3%) (19.7%)</td>
<td>53 (12.4%) (74.7%)</td>
<td>4 (0.9%)</td>
<td>71 (16.7%)</td>
</tr>
<tr>
<td>IV Count (Total %) (Row %)</td>
<td>0</td>
<td>0</td>
<td>1 (0.2%) (100%)</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Total Count (Total %)</td>
<td>23 (5.4%)</td>
<td>185 (43.4%)</td>
<td>211 (49.5%)</td>
<td>7</td>
<td>426 (100%)</td>
</tr>
</tbody>
</table>
Conclusions

• The ADAPT trial is the largest randomized CN trial completed to date.
• One-fifth of patients with mRCC in this trial had baseline stage 3 or worse CKD.
• More than one third of patients randomized to trial developed de novo CKD 3 or worse post CN.
• Older patients with advanced disease may be at higher risk of significant renal insufficiency after CN.
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Questions?
References