Neoadjuvant Therapy in Renal Cell Carcinoma

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Assistant Professor
Department of Urology

MD Anderson Cancer Center
Making Cancer History®

The 9th Congress of the Lebanese Urology Society
Outline

• Case
• Definition
• First report
• Safe?
• Use of neoadjuvant therapy (NAT)?
  – Large → Small?
  – Unresectable → Resectable?
  – Radical → Partial?
  – T3c → T3b or T3b → T3a?
  – In metastatic patients?
• Clinical trial
• Next steps
• Adjuvant Therapy
• Take home messages
Patient 1- At presentation
Patient 2- At presentation
• Preoperative = Presurgical
  – Neoadjuvant (NAT) → Prior to nephrectomy in M0
  – Pseudo-Neoadjuvant (Ψ-NAT) → Prior to nephrectomy in M1
First Report- Sunitinib With Primary Tumor In Place

- 2 Dutch centers
- Retrospective
- 2005-2007
- 17 evaluable patients (primary in situ)
  - 4 PR
  - 12 SD
  - 1 PD
- Median reduction in tumor volume = 31%

van der Veldt AA. Clin Cancer Res. 2008
IS IT SAFE?
Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

John M.L. Ebos1, 2, Christina R. Lee1, William Cruz-Munoz1, Georg A. Bjarnason3, James G. Christensen4 and Robert S. Kerbel1, 2, *
1Molecular and Cellular Biology Research, Sunnybrook Health Sciences Centre, Toronto, ON MN 3M5, Canada
2Department of Medical Biophysics, University of Toronto, Toronto, ON M5G 2M9, Canada
3Sunnybrook Odette Cancer Centre, Toronto, ON M5G 2M9, Canada
4Pfizer Global Research and Development, La Jolla Labs, La Jolla, CA 92121, USA
Sunitinib Does Not Accelerate Tumor Growth in Patients with Metastatic Renal Cell Carcinoma

Krastan B. Blagoev,1,* Julia Wilkerson,2 Wilfred D. Stein,2,3 Robert J. Motzer,4 Susan E. Bates,2 and A. Tito Fojo2,*

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2Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
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http://dx.doi.org/10.1016/j.celrep.2013.01.015
Safety Of Preoperative Targeted Therapy

- Bevacizumab → 20.9% wound dehiscence or delayed wound healing
- Sorafenib → No delayed wound healing, dehiscence, or excessive bleeding
- Sunitinib → 13% delayed wound complication
- Axitinib → 4.2% superficial wound complication
- Pazopanib → 4% delayed wound healing

Sources:
- Jonasch E. J Clin Oncol. 2009
- Cowey CL. J Clin Oncol. 2010
- Karam JA. Eur Urol. 2014
- Rini BI. J Urol. 2015
- Powles T. JAMA Oncol. 2016
Safety Of Preoperative Targeted Therapy

• Retrospective
• All M1 patients
• Stratified by timing of initiation of targeted therapies
  – Pre-operative targeted therapy = 70 patients
  – NO pre-operative targeted therapy = 103 patients
## Safety Of Preoperative Targeted Therapy

<table>
<thead>
<tr>
<th>Event</th>
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<th>Pre-operative Therapy (n=70)</th>
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<tr>
<td>Any Complication</td>
<td>53 (51.4)</td>
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<td>Clavien ≥ 3</td>
<td>32 (30.2)</td>
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<td>Wound Infection</td>
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Chapin B. Eur Urol. 2011
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LARGE $\rightarrow$ SMALL?
Can Preoperative Targeted Therapy Shrink Tumors?

<table>
<thead>
<tr>
<th>Prospective Study</th>
<th>N</th>
<th>Agent</th>
<th>M0 (%)</th>
<th>Clear Cell Histology (%)</th>
<th>Median Diameter Reduction (%)</th>
<th>PR+CR (%)</th>
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</thead>
<tbody>
<tr>
<td>Jonasch 2009</td>
<td>50</td>
<td>Bevacizumab</td>
<td>0</td>
<td>96</td>
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<tr>
<td>Cowey 2010</td>
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<td>56</td>
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<tr>
<td>Silberstein 2010</td>
<td>12</td>
<td>Sunitinib</td>
<td>58</td>
<td>100</td>
<td>21.1 (mean)</td>
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<tr>
<td>Hellenthal 2010</td>
<td>20</td>
<td>Sunitinib</td>
<td>80</td>
<td>100</td>
<td>11.8 (mean)</td>
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<tr>
<td>Powles 2011</td>
<td>66</td>
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<td>0</td>
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<td>6</td>
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<tr>
<td>Rini 2011</td>
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<td>34</td>
<td>75</td>
<td>22</td>
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<td>Karam 2014</td>
<td>24</td>
<td>Axitinib</td>
<td>100</td>
<td>100</td>
<td>28.3</td>
<td>46</td>
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<td>Rini 2015</td>
<td>25</td>
<td>Pazopanib</td>
<td>100</td>
<td>100</td>
<td>24.6</td>
<td>36</td>
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<td>Lane 2015</td>
<td>72</td>
<td>Sunitinib</td>
<td>60</td>
<td>90</td>
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<td>Powles 2016</td>
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<td>Pazopanib</td>
<td>0</td>
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<td>13</td>
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## Summary of Effectiveness in Reducing Tumor Size

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Diameter Reduction (%)</th>
<th>RECIST Response (PR +CR) %</th>
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<tr>
<td>Bevacizumab</td>
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<td>127 (4 studies)</td>
<td>11.8 - 22</td>
<td>5 - 37</td>
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<td>Axitinib</td>
<td>24</td>
<td>23.8</td>
<td>46</td>
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<td>125 (2 studies)</td>
<td>14.4 - 26</td>
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UNRESECTABLE $\rightarrow$ RESECTABLE ?
Sunitinib in “Unresectable” Disease-1

• Retrospective
• 19 patients (15 M1, 10 clear cell RCC) not suitable for nephrectomy
  – Technically unresectable in 12 patients
  – Large metastatic burden in 7
• Median 2 cycles of sunitinib
→ 4 patients underwent nephrectomy
Sunitinib in “Unresectable” Disease-2

- Retrospective
- 10 patients (all M1, clear cell RCC)
- Sunitinib
- Median diameter reduction of 14%

→ 3 patients underwent radical nephrectomy
Sunitinib in “Unresectable” Disease-3

- Prospective
- 30 patients (19 with M1)
- Median 3 cycles sunitinib
- Primary end point → being able to undergo nephrectomy after preoperative sunitinib
- 13 (45%) met the primary end point
  - 4 radical nephrectomy
  - 9 partial nephrectomy

RADICAL NEPHRECTOMY ➔ PARTIAL NEPHRECTOMY?
Sunitinib Prior To Partial Nephrectomy-1

- Prospective
- 20 patients (4 M1, all clear cell RCC)
- 3 months daily sunitinib
  - 12 patients $\rightarrow$ radical nephrectomy
  - 8 patients $\rightarrow$ partial nephrectomy (pT1b-T3a)
- BUT, no mention on how many could have had partial nephrectomy without sunitinib

Hellenthal NJ. J Urol. 2010
Sunitinib Prior To Partial Nephrectomy-2

- Retrospective and prospective pilot
- 12 patients (5 M1, all clear cell RCC)
- Imperative need for partial nephrectomy
- 2 cycles of sunitinib
  - All underwent partial nephrectomy
- BUT, no mention on how many could have had partial nephrectomy without sunitinib

Silberstein JL. BJUI. 2010
Axitinib Prior To Partial Nephrectomy

- Prospective
- 24 patients (cT3a, clear cell, N0M0)
- 12 weeks daily axitinib
  - 5 underwent partial nephrectomy
- BUT, performing partial nephrectomy was not a pre-specified endpoint

Karam JA. Eur Urol. 2014
Pazopanib Prior To Partial Nephrectomy

• Prospective
• 25 patients (all clear cell, M0)
• Imperative need for partial nephrectomy
• Primary endpoint: Radical → Partial
• Tumor size 7.3 cm (range 2.3-10.7)
• Median size decrease → 1.8 cm
• 6 of 13 patients → Partial nephrectomy

Rini Bl. J Urol. 2015
DOWNSTAGE IVC THROMBUS?
## Case Reports

### Targeted Therapy And IVC Thrombus

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial Thrombus Level</th>
<th>Final Thrombus Level</th>
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# Case Reports

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**Cost N. Eur Urol. 2011**
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Targeted Therapy and IVC Thrombus-1

- Retrospective
- 25 patients with IVC thrombus
- Pretreatment biopsy
  - Clear cell RCC → 19 patients
- Targeted therapy (sunitinib in 12)
  - Median of 2 cycles
- IVC tumor thrombus level
  - II = 18
  - III = 5
  - IV = 2

Cost N. Eur Urol. 2011
Change in IVC Thrombus Level

- **21 → Stable**
- **1 → Increase** (level II → III)
- **3 → Decreased** (1 level IV → III, 1 level III → II, and 1 level II → no thrombus)
  - Only one experienced tumor thrombus regression where the surgical approach was potentially affected (level IV to III)
Targeted Therapy and IVC Thrombus-2

- Retrospective
- 14 patients with IVC thrombus
- All clear cell RCC
- Targeted therapy (sunitinib in 11)
  - Median of 2 cycles
- Initial IVC tumor thrombus level
  - I = 1
  - II = 10
  - III = 3

Bigot P. World J Urol. 2014
Change in IVC Thrombus Level

- **12** → Stable
- **1** → Increase (level III → IV)
- **1** → Decreased (level II → I)
  - Surgical approach was NOT altered

Bigot P. World J Urol. 2014
Targeted Therapy and IVC Thrombus-3

• Retrospective
• 22 patients with IVC thrombus (17 were M1)
  – Clear cell → 18 patients (81.8%)
• Targeted therapy (sunitinib in 18, sorafenib in 4)
  – 12 weeks
• Initial IVC tumor thrombus level
  – I = 5
  – II = 2
  – III = 13
  – IV = 2

Kwon T. J Cancer Res Clin Oncol. 2014
Change in IVC Thrombus Level

- Using RECIST
  - 2 → Partial Response
  - 20 → Stable Disease
USE IN METASTATIC PATIENTS?
Presurgical Therapy as “Litmus” Test

50 patients
Single arm prospective study
Metastatic disease
No prior nephrectomy or therapy

Primary Endpoints = TTP, safety
Secondary Endpoints = RR, OS, response duration

Bevacizumab
X 8 weeks

- PR or SD
  - Nephrectomy
  - Continue Bev
- PD
  - Good PS
    - Nephrectomy
    - New drug
  - Poor PS
    - NO Nephrectomy
    - New drug or BSC

Jonasch E. J Clin Onc. 2009
Presurgical Therapy as “Litmus” Test

- Median PFS = 11 months
- Median OS = 25.4 months
- PD = 20%
- PR+CR+SD = 70%
- 50 patients total
  - 42 underwent nephrectomy
  - 8 did not have nephrectomy
    - 6 due to clinical or radiographic progression
Most Recent Presurgical Trial

- 104 patients $\rightarrow$ 100 assessable for clinical benefit
- Preoperative pazopanib for 12-14 weeks
- Primary Endpoint: Clinical Benefit Rate (PR+SD)
- MSKCC Risk
  - Intermediate: 82%
  - Poor: 18%
- ECOG PS 0-1: 91.1%

Powles T. JAMA Oncol. 2016
Results

- PR: 13%
- SD: 71%
- PD: 16%

- Median size reduction of the primary tumor → 14.4%
- Median PFS → 7.1 months
- Median OS → 22.7 months

Powles T. JAMA Oncol. 2016
Clinical Benefit

• Patients achieved clinical benefit?
  – No → Median OS 3.9 months
  – Yes → Median OS 24.0 months
    • HR = 3.92 [95% CI, 1.78-8.63]
Surgical Patients

• 63 patients underwent surgery
• Surgical complications → 14 (22%)
  – Bleeding → 5 (8%)
  – Delayed wound healing → 4 (6%)
  – Splenectomy → 2 (3%)

• 2 complications were Clavien-Dindo grade 3 or 4 and 1 was grade 5

Powles T. JAMA Oncol. 2016
Outcomes in MSKCC Poor-Risk Patients

- 18 patients
  - Median PFS: 3.9 months
  - Median OS: 5.9 months

Powles T. JAMA Oncol. 2016
Conclusions

• Pazopanib appears to be safe preop
• Minimal reduction in primary tumor size
• Outcomes are poor in MSKCC poor-risk patients

Powles T. JAMA Oncol. 2016
Presurgical Immunotherapy Trial - MD Anderson (PI: P. Sharma)

60 patients
Resectable
Randomized- 3 arms

Metastatic Clear Cell RCC

Nivolumab
Nephrectomy
Nivo

Nivolumab + Bevacizumab
Nephrectomy
Nivo

Nivolumab + Ipilimumab
Nephrectomy
Nivo

ClinicalTrials.gov Identifier: NCT02210117
Presurgical Immunotherapy Trial - MD Anderson (PI: P. Sharma)

• Primary Objective:
  – Safety and tolerability of presurgical therapy

• Secondary Objectives:
  – Efficacy of presurgical therapy in RCC (RR, PFS)
  – Immunological changes in tumor tissues and peripheral blood in response to presurgical therapy

ClinicalTrials.gov Identifier: NCT02210117
PHASE II TRIAL OF NEOADJUVANT AXITINIB IN LOCALLY ADVANCED RENAL CELL CARCINOMA
Phase II Trial of Neoadjuvant Axitinib in Locally Advanced Renal Cell Carcinoma

- T2-T3b Clear Cell RCC (biopsy proven)
- PS 0-1
- Acceptable comorbidities

**Primary Endpoint:** Primary Tumor Size Reduction

**Secondary Endpoints:**
- Safety and Toxicity
- Disease Free Survival
- Molecular Correlates

**Site:** MD Anderson (Investigator-Initiated Trial)

**Sponsor:** Pfizer

**Target:** 24 patients

Karam JA. Eur Urol. 2014
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>24</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>60 (42-83)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Clear cell RCC (biopsy)</td>
<td>24</td>
</tr>
</tbody>
</table>

Karam JA. Eur Urol. 2014
## Surgery

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>24</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td></td>
</tr>
<tr>
<td>Radical</td>
<td>19</td>
</tr>
<tr>
<td>Partial</td>
<td>5</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>19</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>5</td>
</tr>
<tr>
<td>Operative time, minutes (range)</td>
<td>87 (56-128)</td>
</tr>
<tr>
<td>Blood loss, cc (range)</td>
<td>225 (25-3,500)</td>
</tr>
</tbody>
</table>
# Pathology Findings

<table>
<thead>
<tr>
<th>Pathologic Stage</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>3</td>
</tr>
<tr>
<td>T1b</td>
<td>1</td>
</tr>
<tr>
<td>T2b</td>
<td>1</td>
</tr>
<tr>
<td>T3a</td>
<td>18</td>
</tr>
<tr>
<td>T4</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Fuhrman grade</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
Response to Axitinib (using RECIST)

- PR → 11 patients
- SD → 12 patients
- PD → None
- Treatment stopped early due to AE → 1 patient
Tumor Size (cm) Change During Axitinib Treatment

Karam JA. Eur Urol. 2014
Percentage Tumor Size Change at 12 Weeks

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Tumor Size Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>-60</td>
<td></td>
</tr>
<tr>
<td>-50</td>
<td></td>
</tr>
<tr>
<td>-40</td>
<td></td>
</tr>
<tr>
<td>-30</td>
<td></td>
</tr>
<tr>
<td>-20</td>
<td></td>
</tr>
<tr>
<td>-10</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

SD, PR

Karam JA. Eur Urol. 2014
INTEROBSERVER AGREEMENT ON
FEASIBILITY OF PARTIAL NEPHRECTOMY
AFTER TARGETED THERAPY
Interobserver Agreement on Feasibility of PN after Targeted Therapy

- 22 paired pre and post axitinib (from Karam JA. Eur Urol. 2014)
- 5 independent reviewers
  - Blinded
  - Pre and post axitinib CT scans
- K-statistic: 0.611
- Of 17 tumors with high complexity before axitinib treatment → 3 became moderate complexity after treatment

Karam JA. BJU Int. 2015
Interobserver Agreement on Feasibility of PN after Targeted Therapy

• *After* treatment with axitinib, all 5 reviewers agreed that
  – only 5 patients required RN (instead of eight *before* treatment)
  – 10 patients could now undergo PN (instead of three *before* treatment)

• The odds of PN feasibility were 22.8-times higher after treatment with axitinib
HOW DOES THE TUMOR PSEUDOCAPSULE CHANGE WITH AXITINIB
## Tumor Pseudocapsule Changes with Axitinib

<table>
<thead>
<tr>
<th></th>
<th>Axitinib</th>
<th>Control</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pseudocapsule present</td>
<td>23/23</td>
<td>23/23</td>
<td></td>
</tr>
<tr>
<td>Thickness of <strong>EXTRARENAL</strong> pseudocapsule, median, mm</td>
<td>2.6 (0.9-5.2)</td>
<td>0.8 (0.3-2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thickness of <strong>INTRARENAL</strong> pseudocapsule, median, mm</td>
<td>1.6 (0.4-3.3)</td>
<td>1.0 (0.3-1.8)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pseudocapsule with irregular thickness</td>
<td>16/23</td>
<td>9/23</td>
<td>0.0746</td>
</tr>
</tbody>
</table>

Kawakami F, ..., Karam JA. J Urol. In press
Pseudocapsule

Kawakami F,..., Karam JA. J Urol. In press
Tumor Pseudocapsule Changes with Axitinib

• Tumor pseudocapsule becomes more irregularly thick after neoadjuvant axitinib
• Axitinib does not affect the frequency of infiltrative tumor invasion to the outside of the pseudocapsule, or the degree of atrophic/inflammatory change in the tumor surrounding tissue
• Technique of PN does not necessarily need to be altered in the context of neoadjuvant therapy
→ One should exercise care to obtain a clearly negative histologic margin in these tumors

Kawakami F,..., Karam JA. J Urol. In press
DOES AXITINIB TREATMENT CAUSE SARCOPENIA?
# Changes with Axitinib Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Median</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>Pre-treatment</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 weeks</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>4.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Pre-treatment</td>
<td>92.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 weeks</td>
<td>89.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>87.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Pre-treatment</td>
<td>30.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 weeks</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>28.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Chery L,..., Karam JA. Urol Oncol. In press
Changes with Axitinib Treatment

Pre-treatment CT scan  7-week CT scan  12-week CT scan

Dark blue = visceral adipose tissue
Red = skeletal muscle
Light blue = subcutaneous adipose tissue
Green = intramuscular adipose tissue
Orange = skin

Chery L,..., Karam JA. Urol Oncol. In press
## Changes with Axitinib Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Median</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skeletal Muscle (cm²/m²)</strong></td>
<td>Pre-treatment</td>
<td>56.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 weeks</td>
<td>51.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>49.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Visceral adipose (cm²/m²)</strong></td>
<td>Pre-treatment</td>
<td>75.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 weeks</td>
<td>73.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>66.8</td>
<td>0.132</td>
</tr>
<tr>
<td><strong>Subcutaneous adipose (cm²/m²)</strong></td>
<td>Pre-treatment</td>
<td>72.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 weeks</td>
<td>68.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>68.1</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Chery L,..., Karam JA. Urol Oncol. In press
Response To Axitinib Treatment Stratified By Sarcopenia Status

<table>
<thead>
<tr>
<th>Sarcopenia</th>
<th>SD N (%)</th>
<th>PR N (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Initial status</td>
<td>Yes</td>
<td>6 (50.0)</td>
<td>1 (9.1)</td>
<td>Reference</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>6 (50.0)</td>
<td>10 (90.0)</td>
<td>10.00</td>
<td>0.96 – 104.49</td>
</tr>
<tr>
<td>Over course of treatment</td>
<td>Never</td>
<td>4 (33.3)</td>
<td>7 (63.6)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial</td>
<td>6 (50.0)</td>
<td>1 (9.1)</td>
<td>0.10</td>
<td>0.01 – 1.10</td>
</tr>
<tr>
<td></td>
<td>Developed</td>
<td>2 (16.7)</td>
<td>3 (27.3)</td>
<td>0.86</td>
<td>0.10 – 7.51</td>
</tr>
</tbody>
</table>

Chery L, ..., Karam JA. Urol Oncol. In press
Patient 1

At presentation
Patient 1

At presentation  After 12 wks axitinib
Patient 2

At presentation
Patient 2

At presentation  After 12 wks axitinib
Framework for Translational Studies

- **At presentation:**
  - Imaging
  - Renal biopsy tissue
  - Serum, plasma, PBMC, urine

- **During axitinib treatment:**
  - Imaging
  - Serum, plasma, PBMC, urine

- **At surgery:**
  - Nephrectomy/LN tissue

- **After surgery:**
  - Serum, plasma, PBMC, urine
CASE
Currently

- 13 cm → Axitinib 3 months → 6.7cm
Take Home Messages

- Safe?
Take Home Messages

- Safe? Yes (wound complications)
Take Home Messages

• Safe? Yes (wound complications)
• Shrink primary renal tumors?
Take Home Messages

- Safe? Yes (wound complications)
- Shrink primary renal tumors? Yes
Take Home Messages

• Safe? Yes *(wound complications)*
• Shrink primary renal tumors? Yes
• Radical → Partial?
Take Home Messages

• Safe? Yes (wound complications)
• Shrink primary renal tumors? Yes
• Radical → Partial? Sometimes
Take Home Messages

• Safe? Yes (wound complications)
• Shrink primary renal tumors? Yes
• Radical → Partial? Sometimes
• Unresectable → Resectable?
Take Home Messages

• Safe? Yes (wound complications)
• Shrink primary renal tumors? Yes
• Radical → Partial? Sometimes
• Unresectable → Resectable? Sometimes
Take Home Messages

• Safe? Yes (wound complications)
• Shrink primary renal tumors? Yes
• Radical → Partial? Sometimes
• Unresectable → Resectable? Sometimes
• Downstage IVC thrombi?
Take Home Messages

• Safe? Yes (wound complications)
• Shrink primary renal tumors? Yes
• Radical → Partial? Sometimes
• Unresectable → Resectable? Sometimes
• Downstage IVC thrombi? Rarely
Take Home Messages

• Safe? Yes (wound complications)
• Shrink primary renal tumors? Yes
• Radical → Partial? Sometimes
• Unresectable → Resectable? Sometimes
• Downstage IVC thrombi? Rarely
• Should we use it *routinely* off-trial?
Take Home Messages

- Safe? Yes *(wound complications)*
- Shrink primary renal tumors? Yes
- Radical → Partial? *Sometimes*
- Unresectable → Resectable? *Sometimes*
- Downstage IVC thrombi? *Rarely*
- Should we use it *routinely* off-trial? *Most definitely NOT!*

*MD Anderson Cancer Center*
Take Home Messages

• Safe? Yes (wound complications)
• Shrink primary renal tumors? Yes
• Radical → Partial? Sometimes
• Unresectable → Resectable? Sometimes
• Downstage IVC thrombi? Rarely
• Should we use it routinely off-trial? Most definitely NOT!
• Can it help selected patients?
Take Home Messages

- Safe? Yes (wound complications)
- Shrink primary renal tumors? Yes
- Radical → Partial? Sometimes
- Unresectable → Resectable? Sometimes
- Downstage IVC thrombi? Rarely
- Should we use it *routinely* off-trial? Most definitely NOT!
- Can it help *selected* patients? Yes
To Do List

• Better define what is “unresectable”
• Better define what is “not amenable to partial nephrectomy”
• Find *predictors of response* to preoperative targeted therapy
  – Collect biopsy, nephrectomy tissue, blood, urine
• Better understand the *utility* of preoperative targeted therapy
  – Multi-institutional randomized trials
Adjuvant Therapy in Renal Cell Carcinoma

Jose A. Karam, MD, FACS
Assistant Professor
Department of Urology
Adjuvant Therapy Trials

• **Ongoing:**
  – **SORCE**: Sorafenib 3 yr vs Sorafenib 1 yr vs Placebo
  – **PROTECT**: Pazopanib vs Placebo
  – **EVEREST**: Everolimus vs Placebo
  – **ATLAS**: Axitinib vs Placebo

• **Negative:**
  – **ARISER**: Rencarex (Girentuximab) vs Placebo
  – **ASSURE**: Sunitinib vs Sorafenib vs Placebo

• **Positive (Pfizer press release, no presentation/manuscript yet):**
  – **S-TRAC**: Sunitinib vs Placebo
Adjuvant Therapy Trials

• Planned:
  – SUO-CTC (sponsored by Genentech/Roche): Atezolizumab vs Placebo in ccRCC patients
  – ECOG-ACRIN 8143 (sponsored by BMS): Nivolumab then nephrectomy then nivolumab vs Nephrectomy only

• Issues with accrual with placebo control arm???
Adjuvant Therapy in RCC

• As of October 1\textsuperscript{st} 2016, there is \textbf{NO ROLE} for adjuvant therapy in RCC
• Awaiting presentation of S-TRAC trial in ESMO (October 2016) and peer-reviewed publication
• What will happen to planned immunotherapy trials?
Figure 1 Study Schema

**Key Eligibility Criteria**
- High risk (Leibovich score ≥ 6) OR
  - intermediate risk (Leibovich score = 5) OR
  - s/p metastasectomy (R0 resection)
- s/p resection ≤ 16 weeks
- No evidence of residual disease
- PD-L1 selected (IC 1/2/3)
- Clear cell or sarcomatoid histology
- No prior adjuvant therapy

**Stratification Factors:**
- Risk (intermediate vs. high vs. metastasectomy)
- Geographic region (North America vs. ROW)
- Sarcomatoid histology (presence vs. absence)

1:1 Randomization

**Arm A**
- Atezolizumab IV 1200 mg q3w × sixteen cycles or 1 year (whichever occurs first)

**Arm B**
- Placebo IV q3w × sixteen cycles or 1 year (whichever occurs first)

IC = tumor-infiltrating immune cell; IV = intravenous; PD-L1 = programmed death ligand-1; q3w = every 3 weeks; s/p = status post; ROW = rest of world.
Clinical stage: \( \geq T2 \) (7cm renal mass) or \( T_{\text{any}N^+} \)

N=766

Randomize

1:1

Nivolumab q 2 wks x 2 doses → Nephr. → Nivolumab q 2 wks X 9 mos

Biopsy (select centers):
- Histology
- PD-L1 expression
- Immune cell infiltration
- Biopsy = Nephr?

*Stratify by cT2 or >cT2, ECOG PS 0 or 1, cN0 or cN+

- Primary endpoint: 13% absolute benefit in recurrence-free survival (RFS)
  - 84.9% power to increase RFS from 55.8% \( \rightarrow \) 68.8% at 5 yrs
- Secondary endpoint OS: 5 yr OS: 78.7% to 87.3%; HR 0.77
- Adequate power to detect 43.5% reduction in risk of death at 5.5 yrs
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  – Bryan Fellman

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  – Gordon Mills
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