RCC Stage at Diagnosis

- 45% Localized disease
- 30% Metastatic disease
- 25% Locally advanced disease

Human Renal Epithelial Neoplasms

<table>
<thead>
<tr>
<th>Type</th>
<th>Clear Cell</th>
<th>Papillary Type 1</th>
<th>Papillary Type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>VHL</td>
<td>Met</td>
<td>FH</td>
<td>BHD</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>75%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Paradigm shift in mRCC in the last 5 years

- Six new agents approved based on increased efficacy over IFN-α or placebo:

<table>
<thead>
<tr>
<th>Comparator</th>
<th>IFN-α</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sunitinib(^1,2)</td>
<td>Sorafenib(^3)</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab(^4,5)</td>
<td>Everolimus(^6)</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus(^7)</td>
<td>Pazopanib(^8)</td>
</tr>
</tbody>
</table>

- IFN-α monotherapy is no longer considered the standard of care in mRCC

What we know

- RCC is inherently VEGF-driven and responsive to targeting of the VEGF pathway
  - mTOR biology relevance less certain although clinical effects of mTOR-targeted therapy are seen

- Clear OR and PFS advantage (vs. IFN/placebo) to VEGF-targeted therapy and substantial OS (2+ years)
  - Sunitinib, pazopanib and Bev/IFN are front-line SOC

- Debulking nephrectomy remains a standard of care (although being re-tested with modern drugs)

- Combination therapy has been toxic / ineffective to date
## Summary of First-Line Phase III Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control</th>
<th>Study Design</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab + IFN-α&lt;sup&gt;1&lt;/sup&gt;</td>
<td>IFN-α</td>
<td>Randomized 1:1, patients previously untreated (AVOREN/CALGB)</td>
<td>31/26 vs 13</td>
<td>10.2 vs 5.4 (HR=0.63, (P&lt;0.0001))</td>
<td>23 vs 21 (HR=0.86, (P=0.1291))</td>
</tr>
<tr>
<td>Sunitinib&lt;sup&gt;2,3,6&lt;/sup&gt;</td>
<td>IFN-α</td>
<td>Randomized 1:1, patients previously untreated</td>
<td>39 vs 8* 47 vs 12&lt;sup&gt;†&lt;/sup&gt;</td>
<td>11 vs 5 (HR=0.42; (P&lt;0.001))</td>
<td>26 vs 22&lt;sup&gt;‡&lt;/sup&gt; (HR=0.82; (P=0.051))</td>
</tr>
<tr>
<td>Pazopanib&lt;sup&gt;6,7&lt;/sup&gt;</td>
<td>Placebo</td>
<td>Randomized 2:1, patients previously untreated or 1 prior cytokine</td>
<td>30 vs 3</td>
<td>9.2 vs 4.2 (HR=0.46; (P&lt;0.001))</td>
<td>23 vs 20.5 HR=0.91 ((p=0.224))</td>
</tr>
<tr>
<td>Sorafenib&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Placebo</td>
<td>Randomized 1:1, patients previously treated with IL-2 or IFN</td>
<td>10 vs 2</td>
<td>5.5 vs 2.8 (HR=0.44; (P&lt;0.01))</td>
<td>19.3 vs 15.9 (HR=0.77; (P=0.02))</td>
</tr>
<tr>
<td>Temsirolimus&lt;sup&gt;4&lt;/sup&gt;</td>
<td>IFN-α</td>
<td>Randomized 1:1:1, patients previously untreated who have poor prognosis</td>
<td>8.6 vs 4.8</td>
<td>5.5 vs 3.1</td>
<td>10.9 vs 7.3 (HR=0.73; (P=0.008))</td>
</tr>
</tbody>
</table>

---

*Independent review.
<sup>1</sup>Investigator.
<sup>2</sup>Log-rank.

Progression-Free Survival

(Independent Central Review)

**Sunitinib**
- Median: 11 months (95% CI: 10–12)

**IFN-α**
- Median: 5 months (95% CI: 4–6)

**Hazard Ratio = 0.415**
- (95% CI: 0.320–0.539)
- *P* < 0.000001

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Progression Free Survival Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>0.1</td>
</tr>
<tr>
<td>10</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**No. at Risk Sunitinib:**
- 235
- 90
- 32
- 2

**No. at Risk IFN-α:**
- 152
- 42
- 18
- 0
Final Overall Survival

Sunitinib (n=375)
Median: 26.4 months
(95% CI: 23.0 - 32.9)

IFN-α (n=375)
Median: 21.8 months
(95% CI: 17.9 - 26.9)

Hazard Ratio = 0.821
(95% CI: 0.673 - 1.001)
p =0.051 (Log-rank)

Total Death
Sunitinib 190
IFN-α 200
OS in patients who did not receive any post-study treatment

- **Sunitinib (n=193)**
  - Median 28.1 months
  - (95% CI: 19.5 - NA)

- **IFN-α (n=162)**
  - Median 14.1 months
  - (95% CI: 9.7 - 21.1)

Hazard Ratio = 0.647
(95% CI: 0.483 - 0.870)
p = 0.0033 (Log-rank)

*Includes 20 patients who crossed over to sunitinib on study*
# PFS in Untreated RCC by Risk Group

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>PFS (mos)</th>
<th>Good</th>
<th>Int</th>
<th>Poor</th>
<th>HR vs. IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>11</td>
<td>14.5</td>
<td>10.6</td>
<td>3.7</td>
<td>0.54</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>11.1</td>
<td></td>
<td></td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>(vs. placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bev + IFN (AVOREN)</td>
<td>10.2</td>
<td>12.9</td>
<td>10.2</td>
<td>2.2</td>
<td>0.63</td>
</tr>
<tr>
<td>Bev + IFN (CALGB)</td>
<td>8.5</td>
<td>11.1</td>
<td>8.4</td>
<td>3.3</td>
<td>0.71</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>5.7</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>0.88</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>3.7</td>
<td>NA</td>
<td>NA</td>
<td>3.7*</td>
<td>NR</td>
</tr>
</tbody>
</table>

* Included 31% of pts classified as intermediate risk per MSKCC

2. Escudier, et al. JCO, 2009
## Overall Survival in Untreated RCC by Risk Group

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>OS (mos)</th>
<th>Good</th>
<th>Int</th>
<th>Poor</th>
<th>HR vs. IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>26.4</td>
<td>Not reached**</td>
<td>20.7</td>
<td>5.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>21.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bev + IFN (AVOREN)</td>
<td>23.3</td>
<td>35.1</td>
<td>22.6</td>
<td>6.0</td>
<td>0.86</td>
</tr>
<tr>
<td>Bev + IFN (CALGB)</td>
<td>18.3</td>
<td>32.5</td>
<td>17.7</td>
<td>6.6</td>
<td>0.86</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>10.9</td>
<td>NA</td>
<td>NA</td>
<td>10.9*</td>
<td>0.73</td>
</tr>
</tbody>
</table>

** Median overall survival had not been reached with either treatment in the favorable risk group. At 12 months, 91% of patients in the sunitinib group were alive compared with 92% of patients in the IFN group; and at 2 years, 72% v 76%, respectively, were alive.
What we don’t know

• When do we start therapy for indolent patients?
• Which is the ‘best’ drug for initial therapy?
• Will next-generation, more potent VEGFR TKIs (axitinib/tivozanib) be substantial advances?
What we don’t know

- What is the best way to administer these drugs chronically?

- Mechanisms/biomarkers of response/resistance to targeted therapy?
  - No clear biologic rationale for tx sequences

- Activity of VEGF-targeted therapy in the (neo)/adjuvant setting?
RCC is an Inherently Diverse Disease

% Survival vs Months
When to Start Therapy?

• Our job as RCC doctors is to optimize the timing and type of therapy in order to delay as long as possible a patient from reaching a lethal tumor burden while maintaining maximal quality of life.

• This means that select patients may have inherent ‘control’ of tumor burden and thus immediate systemic treatment is not indicated. Such patients may be served best in the long run with initial surveillance.
**Active Surveillance of the Small Renal Mass: A meta-analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th>N</th>
<th>Mean Lesion Size (cm)</th>
<th>Mean Growth Rate (cm/yr)</th>
<th>Mean F/U Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujimoto et al</td>
<td>Sendai Shakaihoken Hospital Sendia, Japan</td>
<td>6</td>
<td>2.47</td>
<td>0.47</td>
<td>29</td>
</tr>
<tr>
<td>Bosniak et al</td>
<td>NYU Medical Center New York, USA</td>
<td>40</td>
<td>1.73</td>
<td>0.36</td>
<td>39</td>
</tr>
<tr>
<td>Kassouf et al</td>
<td>McGill University Health Center Montreal, Canada</td>
<td>26</td>
<td>3.27</td>
<td>0.09</td>
<td>32</td>
</tr>
<tr>
<td>Volpe et al</td>
<td>Princess Margaret Hospital Toronto, Canada</td>
<td>32</td>
<td>2.48</td>
<td>0.1</td>
<td>35</td>
</tr>
<tr>
<td>Wehle et al</td>
<td>Mayo Clinic Jacksonville, USA</td>
<td>29</td>
<td>1.83</td>
<td>0.12</td>
<td>32</td>
</tr>
<tr>
<td>Kato et al</td>
<td>Tohoku School of Medicine Sendia, Japan</td>
<td>18</td>
<td>1.98</td>
<td>0.42</td>
<td>27</td>
</tr>
<tr>
<td>Sowery et al</td>
<td>Kingston General Hospital Kingston, Canada</td>
<td>22</td>
<td>4.08</td>
<td>0.86</td>
<td>26</td>
</tr>
<tr>
<td>Current Series</td>
<td>Fox Chase Cancer Center Philadelphia, USA</td>
<td>61</td>
<td>2.97</td>
<td>0.20</td>
<td>36</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>234</td>
<td>2.60</td>
<td>0.28</td>
<td>34</td>
</tr>
</tbody>
</table>

*Robert Uzzo  M.D.*

*Uzzo et al. J Urol 175 (2): 425, 2006*
Whom to observe?

- Limited modern data exists.

- Good performance status patients with ‘low-volume’, ‘slow-growing’ and asymptomatic disease are candidates after risk/benefit discussion with the patient.

- A prospective study is underway at The Cleveland Clinic and other centers
  - What is the natural growth rate?
  - What is the clinical outcome when treatment is started?
  - Anxiety/depression associated with observation?
  - Translational studies in untreated population...
How I decide on initial therapy

• I tell the patient:
  – “I don’t know which drug is the best one for YOU”
  – “It’s not so much which one, but which one FIRST. Other drugs don’t go away, they are just put to the side.”
  – I list drug names and general categories

• I make decisions one treatment at a time

• I always consider clinical trial options first

• I consider a patient’s histology, tumor burden/pace, route of administration/co-pay issues, fitness to ‘tolerate’ a given therapy, and of course the clinical data
Phase III non-inferiority trial of pazopanib vs sunitinib in first-line mRCC (COMPARZ)

Eligibility criteria:
- Locally advanced or mRCC with clear-cell histology
- No prior systemic therapy for advanced mRCC

Primary endpoint: PFS
Secondary endpoints: OS, ORR, time to response, duration of response, safety, QoL

PI: Robert J Motzer

www.clinicaltrials.gov (NCT00720941)
Randomized Phase III Trial of Temsirolimus + Bevacizumab vs IFN + Bevacizumab in Metastatic Renal Cell Carcinoma

Patients with metastatic RCC, treatment naïve
N=800

Primary Endpoint: PFS

Temsirolimus + bevacizumab
IFN + bevacizumab
More potent VEGF-R TKIs in RCC

Axitinib in cytokine-refractory RCC

- Objective response rate of 44.2%
- Median response duration was 23.0 months
- Progression-free survival was 13.7 months

Rixe et al. Lancet Oncology 8 (11), 2007
Eligibility criteria:
- Histologically confirmed mRCC with clear-cell component
- Failure of one prior first-line regimen containing ≥1 of:
  - Sunitinib
  - Bevacizumab + IFN-α
  - Temsirolimus
  - Cytokine(s)

Stratification
- Prior regimen
- ECOG PS 0 vs 1

Primary endpoint: PFS
Secondary endpoints: OS, ORR, duration of response, safety, QoL

PI: Brian Rini
www.clinicaltrials.gov (NCT00920816)
Tivozanib Clinical Responses by Independent Radiology Assessment

* Median PFS 11.8 months

TIVO-1 Trial: Phase 3 Head-to-Head Trial of Tivozanib vs Sorafenib

Eligibility requirements:
- Advanced clear cell RCC
- Prior nephrectomy
- No prior VEGF treatment
- ECOG PS 0-1

**Primary endpoint**: PFS

**Secondary endpoints**: overall survival, ORR, quality of life

ClinicalTrials.gov Identifier: NCT01030783, NCT01076010.
Intermittent TKI treatment

- Retrospective series from Germany/Netherlands of pts on TKI (n=12; 11 sunitinib) with CR / surgical CR in whom TKI was stopped, and pts were observed.
  - Median time off therapy was 7.5 months (range, 3-25)
  - 5 with recurrent disease at a median of 6 months (range, 3-8); 1 pt with spinal cord compression at recurrence
  - TKI re-administered with tumor burden reduction in all 5

Holding VEGF Therapy

- 40 mRCC patients with disease control (RECIST SD or better) on VEGF-targeted therapy (median 15 months) observed off therapy

- Twenty five patients (63%) had progression of disease.
  - Median PFS in these patients was 10 (1.4 to 27.2) months.

- Fifteen patients (37%) had stable disease as of ESD documented by staging studies.
  - Median PFS for patients who remained progression-free as of ESD was 8.9 (4.6 to 28.2) months.

Sadeghi et al. KCA 2010 and ASCO GU 2011
CCF Intermittent Sunitinib Study

Metastatic clear cell RCC (n=30) → Sunitinib 50 mg 4/2 x 4 cycles

*NO Tumor burden decrease by 10%*

→ **Continue therapy off study or change therapy if PD**

→ **Tumor burden decrease by 10%**

→ **Hold sunitinib. Restart with 10% increase in tumor burden from nadir**
PISCES Patient Preference Study Design


- **Primary endpoint**
  - Patient preference

- **Secondary endpoints**
  - Quality of life (EQ-5D)
  - Safety (FACIT-Fatigue)
  - Pharmacokinetics
  - Biomarkers

Randomisation

N=160

Pazopanib 800 mg once daily, 10 weeks

Sunitinib 50 mg 4/2, 10 weeks

Sunitinib 50 mg 4/2, 10 weeks

Pazopanib 800 mg once daily, 10 weeks

Patient choice of treatment to progression

2 week washout

Time (weeks)

0 4 10 12 22
Progression-free Survival Grouped by Threshold Week 4 Pazopanib

Kaplan-Meier progression-free survival (PFS) curves for patients with Week 4 pazopanib Cmin > 20.6 μg/mL and ≤ 20.6 μg/mL.

- Median PFS was 49.4 weeks for patients with Week 4 Cmin > 20.6 μg/mL, whereas median PFS was 20.3 weeks for patients with Cmin ≤ 20.6 μg/mL (P = 0.0041).
Time to Tumor Progression on Sunitinib 50mg 4/2 vs. 37.5mg continuous (EFFECT trial) –Dose matters!

**Schedule 4/2 (N=146)**
Median, 9.9 months
(95% CI, 7.0–13.4)

**CDD Schedule (N=146)**
Median, 7.1 months
(95% CI, 6.8–9.7)

HR, 0.77
(95% CI, 0.57–1.04)
P=0.090 (unstratified log-rank test)

Motzer et al. ASCO GU 2011
Resistance to Targeted Therapy in RCC

Cell Stimuli (e.g. growth factors)

Compensatory increase in PI3-K and Akt with mTORC1 inhibition leads to upregulation of mTORC2 and further Akt and HIF activation.

Inactivated VHL tumor suppressor gene

Hypoxia

FKBP

PI3-K

Akt

VHL

HIFα

mTORC1

Raptor

mLST8

4E-BP1

eIF-4E

HIFα

p70S6K

Rictor

MSIN1

HIFα

4E-BP1

eIF-4E

mRNA translation

Cyclin D1

c-Myc

Cell growth and survival

Transcriptional activation of HIF target genes

HIFα

Uregulation of alternative, non-HIF-mediated, pro-angiogenic genes/proteins (e.g. FGF, angiopoietin, IL-8, PIGF).

TUMOR CELL

Bevacizumab

VEGFR

Sunitinib

Sorafenib

Axitinib

Pazopanib

VEGF

PDGF

ENDOTHELIAL CELL

Inadequate target inhibition due to reduced drug levels and/or enhanced receptor signaling.
Resistance Appears Mediated by “Angiogenic Escape” - ASL MRI: Rodent model

- ASL MRI
- H & E
- CD34
## Results in VEGF-targeted Therapy-refractory RCC Patients

<table>
<thead>
<tr>
<th>Agent</th>
<th>Population</th>
<th>N</th>
<th>OR / TS</th>
<th>PFS</th>
</tr>
</thead>
</table>
| Sunitinib  
(Rini et al. *JCO*, 2008) | Phase II: Bevacizumab-refractory                | 62  | 23% / 75%       | 7.1 months        |
| Axitinib  
(Rini et al. *JCO*, 2009) | Phase II: Sorafenib-refractory                  | 62  | 23% / 55%       | 7.4 months        |
| Sorafenib  
(Garcia et al. *Cancer* 2010) | Phase II: Bevacizumab or sunitinib-refractory   | 49  | 0% / 30%        | 4.4 months        |
| Temsirolimus  
(MacKenzie et al. *Ann Oncol*. 2010) | Retrospective study                             | 87  | 5% / n.s.       | 3.9 months        |
| Everolimus  
(Motzer et al. *Lancet*, 2008; *Cancer* 2010) | Phase III: TKI-refractory (vs. placebo)         | 410 | 2% / 60%        | 4.9 months (vs. 1.9 months) |

*Clinical activity is greatest with drugs that more potently inhibit VEGF-R

*More modest clinical effect is seen with mTOR inhibition in this setting, similar to weak VEGF-R inhibition*
Pazopanib in refractory RCC: Progression-free survival (n=41)

Median PFS (months)
All patients: 11.86
Prior sunitinib: 11.86
Prior bevacizumab: 11.93

Hainsworth et al. Annals Oncol 2010; 21(Suppl 8): Abstract 910P and poster
SWITCH: Phase III sequential study of sorafenib and sunitinib

Eligibility
- mRCC with all histologies

Stratification
- ECOG PS 0 or 1
- No prior systemic therapy for advanced or mRCC

Primary endpoints: overall PFS
Secondary endpoints: total time to progression, OS, disease control rate and cardiotoxicity

Sorafenib 400 mg BID
Sunitinib 50 mg/day (Schedule 4/2)

Sunitinib 50 mg/day (Schedule 4/2)
Sorafenib 400 mg BID

Discontinuation (due to progressive disease/toxicity)

Study being conducted in Germany

PI: Dr P Goebell
www.clinicaltrials.gov (NCT00732914)
RECORD-3: Phase II sequential study of sunitinib and everolimus

Eligibility
- Patients with advanced RCC

Stratification
- Karnofsky performance status ≥70%
- No prior systemic therapy for advanced or mRCC

Primary endpoints: first PFS
Secondary endpoints: second PFS, ORR, duration of response, patient-reported outcomes, OS

www.clinicaltrials.gov (NCT00903175)
The Search for Predictive Biomarkers

Cleveland Clinic (1985-2003)
Clinically Localized ccRCC Patients s/p Nephrectomy
n = 2,313

Pathology Re-review

Pathology Exclusions  627 (27%)
- Insufficient tissue
- Histology reclassified upon review

Clinical Re-review

Clinical Exclusions  744 (32%)
- Patients with known or suspected inherited RCC (e.g. VHL) and/or bilateral tumors
- Patients with metastatic disease
- Patients treated with neoadjuvant or adjuvant systemic therapy
- Patients with inadequate follow-up (missing or < 6 months)

Final Evaluable Population
Recurrence Free Interval  n = 931
Overall Survival  n = 942
Dendrogram of Key Gene Groups Associated with Recurrence of Localized RCC after Nephrectomy
Axitinib: OS in patients with or without dBP ≥ 90 mmHg

Lead-in
Axitinib 5mg BID
(1 cycle)

Randomization Criteria:
- sBP<150
- dBP<90
- no grade 3 or 4 axitinib related AE (if on antihypertensive at baseline)

Arm A
Axitinib 5 mg BID + axitinib dose escalation

Arm B
Axitinib 5 mg BID + placebo dose escalation

Arm C
Continue Axitinib 5mg BID or at reduced dose
Sunitinib: Clinical Outcome by HTN Status in RCC Patients

<table>
<thead>
<tr>
<th></th>
<th>Max. SBP ≥140 mmHg (n=442)</th>
<th>Max. SBP &lt;140 mmHg (n=92)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, n (%)</td>
<td>242 (54.8%)</td>
<td>8 (8.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Progression-free survival, months</td>
<td>12.5</td>
<td>2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall survival, months</td>
<td>30.9</td>
<td>7.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Max. DBP ≥90 mmHg (n=363)</th>
<th>Max. DBP &lt;90 mmHg (n=171)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, n (%)</td>
<td>208 (57.3%)</td>
<td>42 (25.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Progression-free survival, months</td>
<td>13.4</td>
<td>5.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall survival, months</td>
<td>32.2</td>
<td>14.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Rini BI et al. JNCI 103 (9), 2011
A

With HTN (n = 354)
Median OS, 31.1 months (95% CI: 27.9 to 35.2)

Without HTN (n = 161)
Median OS, 18.2 months (95% CI: 14.0 to 21.0)

P < .0001

B

With HTN (n = 241)
Median OS, 31.1 months (95% CI: 25.6 to 34.3)

Without HTN (n = 274)
Median OS, 23.0 months (95% CI: 20.3 to 27.9)

P = .013
Does Management of Hypertension Matter?

![Graph showing survival rates with different management strategies.

- Anti-HTN drug only: Median OS, 32.3 months (95% CI: 28.1 to NR)
- Dose reduction only: Median OS, 26.8 months (95% CI: 18.9 to NR)
- Both: Median OS, 33.0 months (95% CI: 27.9 to NR)
- Neither: Median OS, 25.8 months (95% CI: 19.0 to 30.2)
- Without HTN: Median OS, 6.4 months (95% CI: 5.0 to 9.5)

<table>
<thead>
<tr>
<th>Management Strategy</th>
<th>No. of Patients at Risk</th>
<th>Survival Rate (Probability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HTN drug only</td>
<td>113 108 97 79 70 59 52 29 6</td>
<td>1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0</td>
</tr>
<tr>
<td>Dose reduction only</td>
<td>85 77 67 55 46 40 37 17 5</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>157 151 140 125 101 87 72 44 14</td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>87 82 73 49 40 38 29 16 4</td>
<td></td>
</tr>
<tr>
<td>Without HTN</td>
<td>92 55 38 21 15 7 5 3 1</td>
<td></td>
</tr>
</tbody>
</table>
SNPs in *IL8*, *FGFR2*, *VEGFR3*, *VEGFA*, and *NR1I2* Associated with OS in Pazopanib-Treated Patients

<table>
<thead>
<tr>
<th>GENE</th>
<th>SNP (NCBI)</th>
<th>P Value</th>
<th>Allele Frequency Caucasians, %</th>
<th>Allele Frequency Asians, %</th>
<th>Allele Frequency Blacks, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>IL8</em></td>
<td>rs1126647</td>
<td>0.003</td>
<td>39</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td><em>IL8</em></td>
<td>rs4073</td>
<td>0.01</td>
<td>40</td>
<td>35</td>
<td>83</td>
</tr>
<tr>
<td><em>FGFR2</em></td>
<td>rs2981582</td>
<td>0.01</td>
<td>42</td>
<td>25</td>
<td>52</td>
</tr>
<tr>
<td><em>VEGFR3</em></td>
<td>rs307826</td>
<td>0.04</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>VEGFA</em></td>
<td>rs1570360</td>
<td>0.05</td>
<td>25</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td><em>NR1I2</em></td>
<td>rs3814055</td>
<td>0.03</td>
<td>41</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>

- None of the SNPs associated with OS in patients who did not receive pazopanib
- Limitation: small sample size (N = 37)


Presented at the Genitourinary Cancers Symposium
Cox regression: $P=0.055$ OR $=2.51$ (95%CI 0.98-6.41)

Cox regression: $P=0.046$ OR $=2.98$ (95%CI 1.02-8.71)

Response (PD vs CR+PR+SD)

**VEGFR3**

**VEGFR3 rs307821**
- wt/wt
- wt/var
- var/var

Proportion progression free

**VEGFR3 rs307826**
- wt/wt
- wt/var

TTP (days)

$P=0.000002$  
$P=0.019$

Donas JG et al. ESMO 2010
### Pre-surgical VEGF-Targeted Therapy in RCC

<table>
<thead>
<tr>
<th>Approach</th>
<th>Patient population</th>
<th>No. of pts with primary tumor shrinkage</th>
<th>Amount of primary tumor shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sunitinib</strong> <em>(CCF/retrospective)</em></td>
<td>‘Unresectable’ RCC (n=19)</td>
<td>42%</td>
<td>24% (range, 2-46%)</td>
</tr>
<tr>
<td><strong>Sunitinib</strong> <em>(Netherlands/retrospective)</em></td>
<td>M+ pts with primary in place (n=17)</td>
<td>59%</td>
<td>12% (range, 2-33%)</td>
</tr>
<tr>
<td><strong>Sunitinib</strong> <em>(CCF/prospective)</em></td>
<td>‘Unresectable’ RCC (n=18)</td>
<td>72%</td>
<td>19% (range, 1-64%)</td>
</tr>
<tr>
<td><strong>Sorafenib</strong> <em>(UNC/prospective)</em></td>
<td>≥T2 RCC; sorafenib 400 mg BID x 4–8 weeks prior to nephrectomy (n=25)</td>
<td>64%</td>
<td>11% (range, 0–40%)</td>
</tr>
<tr>
<td><strong>Bevacizumab (+/- erlotinib)</strong></td>
<td>Metastatic RCC pts prior to nephrectomy; treatment x 8 weeks (n=50)</td>
<td>52%</td>
<td>~ 10% (range, 1-25%)</td>
</tr>
</tbody>
</table>
• Primary RCC baseline and after 2 cycles of sunitinib: tumor shrinkage enabled partial nephrectomy as the tumor has pulled away from the renal hilum.

• Viable RCC tumor cells were present in all post-sunitinib surgical specimens. No unexpected surgical morbidity was encountered.
A single arm phase II study of pazopanib in patients with localized RCC to enable partial nephrectomy

Patients with localized RCC in whom partial nephrectomy is desired but not currently possible (n=30)

Pazopanib 800 mg QD x 8 - 16 weeks (depending on tumor response)

Tumor amenable to partial nephrectomy

Partial nephrectomy performed after 1 week off pazopanib

Tumor NOT amenable to partial nephrectomy

Radical nephrectomy performed after 1 week off pazopanib
### On-going/Planned Adjuvant RCC phase III Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population/Design</th>
<th>Primary Endpoint</th>
<th>Study Start</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSURE¹ (ECOG)</td>
<td>1923</td>
<td>Placebo vs. sunitinib vs. sorafenib, 1 year</td>
<td>DFS</td>
<td>2006</td>
</tr>
<tr>
<td>SORCE² (MRC)</td>
<td>1656</td>
<td>Placebo vs. sorafenib 1 year vs. sorafenib 3 years</td>
<td>DFS</td>
<td>2007</td>
</tr>
<tr>
<td>S-TRAC³ (Pfizer)</td>
<td>500</td>
<td>Placebo vs. sunitinib 1 year</td>
<td>DFS</td>
<td>2007</td>
</tr>
<tr>
<td>Everest⁴ (SWOG)</td>
<td>1218</td>
<td>Placebo vs. everolimus 1 year</td>
<td>DFS</td>
<td>2010</td>
</tr>
<tr>
<td>PROTECT VEG113387 (GSK)</td>
<td>1500</td>
<td>Placebo vs. pazopanib 1 year</td>
<td>DFS</td>
<td>Q4 2010</td>
</tr>
</tbody>
</table>

2. ClinicalTrials.gov. NCT00492258.  
Autologous Vaccine Phase 3 Trial
Planned for mid-2011

Pre-treatment Phase

- Diagnosis, Screening, Nephrectomy (Nx)

Treatment Phase

- Randomize 1:1
- Leukapheresis

Maintenance Phase

- Sunitinib + AGS-003 (N = 300)
- 1 cycle Sunitinib
- AGS-003 5 doses, 3 wks apart
- AGS-003 quarterly
- Continued Sunitinib

- Sunitinib (N = 300)
  - 1 Sunitinib cycle = 4 weeks on followed by 2 weeks off

• AGS-003 is a vaccine made of dendritic cells loaded with a specific patient's total tumor RNA
IMA901 Renal Cell Cancer Phase 3 trial
Study design of planned IMA901-301 study

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

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)

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

Primary endpoint
- Overall Survival

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

• Therapy targeted at VEGF and mTOR has dramatically changed the therapeutic landscape of metastatic RCC.

• There is no single drug as best choice for initial therapy pending future trials.

• I believe more potent VEGFR TKIs will be substantial clinical advances.

• Intermittent therapy or other novel administration methods warrant investigation.
Conclusions

- Mechanisms/biomarkers that underlie response/resistance to targeted therapy remain elusive but preliminary data exists and intense efforts are underway.

- The activity/utility of VEGF-targeted therapy in the (neo)/adjuvant setting awaits further investigation.
## RCC Treatment Algorithm: 2011

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Therapy (level 1)</th>
<th>Other Options (≥ level 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>Good or Intermediate risk</td>
<td>Sunitinib, Bevacizumab + IFN, Pazopanib</td>
<td>HD IL-2, Sorafenib, Clinical trial, Observation</td>
</tr>
<tr>
<td></td>
<td>Poor risk</td>
<td>Temsirolimus</td>
<td>Sunitinib, Bev/IFN, Clinical trial</td>
</tr>
<tr>
<td></td>
<td>Non-clear cell</td>
<td></td>
<td>Anything, Clinical Trial</td>
</tr>
<tr>
<td></td>
<td>Sarcomatoid</td>
<td></td>
<td>Sunitinib (+- Gem), Clinical trial</td>
</tr>
<tr>
<td>Refractory</td>
<td>Cytokine</td>
<td>Sorafenib</td>
<td>Sunitinib, Bevacizumab</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>Everolimus</td>
<td>Everything</td>
</tr>
<tr>
<td></td>
<td>mTOR</td>
<td>Clinical trial</td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

*Note: Axitinib is used in refractory settings for sarcomatoid and mTOR.*