Evidenze cliniche nel trattamento del RCC

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Unità Sperimentazioni Cliniche
Istituto Nazionale Tumori di Napoli

Napoli, 14 ottobre 2008
The past...

IL-2, interferon
IL-2 and IFN in metastatic RCC

• **IL-2**
  – Responses: 15%
  – CR: 5% (durable)
  – Survival benefit: not demonstrated in prospective trials
  – Toxicity: significant (high dose...)

• **IFN**
  – Responses: 10%
  – CR: 2%
  – Survival benefit: increased median survival reported
  – Toxicity: dose correlated...
Advances in last years

- In understanding the biology and genetics of renal cell carcinoma
- Availability of novel targeted approaches for the treatment of metastatic RCC
VHL Gene Mutation in Clear-Cell RCC

- VHL gene mutation: 60%
- Hypermethilation: 20%
- VHL complex disrupted
- HIF accumulation
- Angiogenesis

Brugarolas, NEJM 2007
New target-based agents

- Temsirolimus
- Everolimus
- Sunitinib
- Sorafenib
- Bevacizumab

Brugarolas, NEJM 2007
Target-based agents in RCC: phase 3 trials

- Inhibitors of VEGF receptors
- Monoclonal antibody directed against VEGF
- Inhibitors of mTOR
Inhibitors of VEGF receptors

Morabito A, The Oncologist 2006
Sunitinib (SU11248)
Sunitinib: phase 2 trials in RCC

- Two sequentially conducted multicenter phase 2 trials in second-line therapy
- Endpoint: response rate
- Overall response: **40%** and **34%**
- Stable disease: 28% and 23%

Motzer RJ, J Clin Oncol 2006; Motzer RJ, JAMA 2006
Sunitinib: Phase III Trial for first-line treatment of advanced RCC

Study Design: Randomized, Multicenter Trial (Enrollment Complete)

 Patients with treatment-naïve mRCC (N=750)
1:1 randomization

Sunitinib 4 wk on/2 wk off: 50 mg/d

n=375

IFN-α (subcutaneous): 9 MU tiw

n=375

Primary end-point: Progression-Free Survival

Progression-Free Survival


Median PFS: 11 vs 5 months

Hazard ratio, 0.42; 95% CI, 0.32–0.54; P<0.001

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Sunitinib</th>
<th>Interferon alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>375</td>
<td>375</td>
</tr>
<tr>
<td>12</td>
<td>235</td>
<td>152</td>
</tr>
<tr>
<td>24</td>
<td>90</td>
<td>42</td>
</tr>
<tr>
<td>28</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>32</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Overall Survival

p-value: 0.0128 (Wilcoxon)

(more appropriate test when the ratio of death rates between two treatment groups is not constant over time in situations where survival data may be confounded by crossover or post-study treatments)

Figlin R, ASCO 2008
Quality of Life in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib or Interferon Alfa: Results From a Phase III Randomized Trial

David Cella, Jim Z. Li, Joseph C. Cappelleri, Andrew Bashmakin, Claudie Charbonneau, Sindy T. Kim, Ison Chen, and Robert J. Motzer

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Sunitinib</th>
<th>IFN-α</th>
<th>Difference</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FKS-IDRS</td>
<td>29.4</td>
<td>27.4</td>
<td>1.98</td>
<td>1.46 to 2.51</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>FKS-15</td>
<td>45.3</td>
<td>42.1</td>
<td>3.27</td>
<td>2.36 to 4.18</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>FACT-G</td>
<td>82.3</td>
<td>76.8</td>
<td>5.58</td>
<td>3.91 to 7.24</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>PWB</td>
<td>21.3</td>
<td>19.9</td>
<td>1.42</td>
<td>0.796 to 2.04</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>SFWB</td>
<td>23.5</td>
<td>22.3</td>
<td>1.20</td>
<td>0.667 to 1.73</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>EWB</td>
<td>18.3</td>
<td>17.5</td>
<td>0.787</td>
<td>0.323 to 1.25</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>PWB</td>
<td>19.0</td>
<td>17.0</td>
<td>1.98</td>
<td>1.33 to 2.63</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>EQ-5D Index</td>
<td>0.762</td>
<td>0.725</td>
<td>0.0364</td>
<td>0.0109 to 0.0620</td>
<td>.0052</td>
</tr>
<tr>
<td>EQ-VAS</td>
<td>73.4</td>
<td>68.7</td>
<td>4.74</td>
<td>2.60 to 6.87</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
Sunitinib: conclusions

- Sunitinib has consistently demonstrated improvements in progression-free survival, response rate and overall survival compared to IFN-α.
- Sunitinib provided superior QoL compared with IFN-in mRCC patients.
- Sunitinib is the reference standard for the first-line treatment of mRCC.

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>Setting</th>
<th>Pts</th>
<th>PFS (months)</th>
<th>OR (%)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzer (NEJM, 2007)</td>
<td>Sunitinib vs IFN</td>
<td>1st line</td>
<td>750</td>
<td>11 vs 5 (p&lt;0.0001)</td>
<td>31 vs 6 (p&lt;0.001)</td>
<td>HR: 0.65 (p=0.02)*</td>
</tr>
</tbody>
</table>
Sorafenib
Methods

- **Study design:** randomized discontinuation trial
- **Primary end-point:** progression-free survival (PFS) at 12 weeks
Patient flow

RCC

Sorafenib 12-week run-in (n=202)

Tumour Shrinkage ≥25% (n=73)

Continue sorafenib open label (n=79)

Tumour growth/Shrinkage <25% (n=69)

Sorafenib 12 weeks (n=32)

Placebo* 12 weeks (n=33)

Tumour growth/≥25% (n=51†)

% progression free at 24 weeks

Off study (n=58)

Disease status at 12 weeks unknown (n=9)

*Placebo patients who progressed could cross over to sorafenib
†including 36 patients without bidimensional tumor measurements, but with radiological evidence of progression

Ratain, ASCO 2005
Randomized discontinuation trial

- It is a rational phase II study design to demonstrate activity of a possibly cytostatic agent in a disease having substantial patient-to-patient variation in tumor growth rates, and for which disease stabilization is a clinically meaningful measure of activity

Rosner et al. JCO 2002
Sorafenib: phase 2 results

- **PFS at 12 weeks**: 50% with sorafenib vs 18% with placebo (p=0.0077)
- **Median PFS**: 24 weeks with sorafenib vs 6 weeks with placebo (p=0.0087)

![Kaplan-Meier plot of investigator-assessed progression-free survival from week 12 randomization for patients randomized to placebo (n = 33) or to sorafenib (n = 32).](image)
Sorafenib: Phase III Trial for cytokine pretreated advanced RCC

Eligibility criteria:
- Histologically/cytologically confirmed, unresectable and/or metastatic disease
- Clear cell histology
- Measurable disease
- Failed one prior systemic therapy in last 8 months
- ECOG PS 0 or 1
- Good organ function
- No brain metastasis
- Poor risk Motzer group excluded

(1:1) Randomization n~884

Stratification
- Motzer criteria
- Country

Sorafenib 400 mg bid

Placebo

Major endpoints
- Survival (alpha=0.04)
- PFS (alpha=0.01)
Progression-free and overall survival

Sorafenib for older patients: subset analysis

Eisen T, JNCI 2008
### Sorafenib: conclusions

- Sorafenib has demonstrated improvements in PFS compared to placebo.
- Sorafenib is the reference **standard for the second-line** treatment of cytokine pretreated mRCC.

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>Setting</th>
<th>Pts</th>
<th>PFS (months)</th>
<th>OR (%)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escudier (NEJM, 2007)</td>
<td>Sorafenib vs Placebo</td>
<td>2\textsuperscript{nd} line</td>
<td>903</td>
<td>5.5 vs 2.8 (p&lt;0.001)</td>
<td>10 vs 2 (p&lt;0.001)</td>
<td>HR: 0.72 (p=0.02)</td>
</tr>
</tbody>
</table>
Monoclonal antibody directed against VEGF

A Randomized Trial of Bevacizumab, an Anti–Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer

James C. Yang, M.D., Leah Haworth, B.S.N., Richard M. Sherry, M.D., Patrick Hwu, M.D., Douglas J. Schwartzentruber, M.D., Suzanne L. Topalian, M.D., Seth M. Steinberg, Ph.D., Helen X. Chen, M.D., and Steven A. Rosenberg, M.D., Ph.D.

• **Methods**
  – **Design:** randomized, double-blind, phase 2 trial, comparing placebo with bevacizumab at doses of 3 and 10 mg per kilogram of body weight, given every two weeks
  – **Primary end-point:** TTP (time to progression of disease)
p<0.01

RO = 10%
(95% CI: 2.9-24.2%)

p=0.041

RO = 0%

Figure 1. Kaplan–Meier Analysis of Survival Free of Tumor Progression for Patients Receiving High-Dose Bevacizumab (Panel A) or Low-Dose Bevacizumab (Panel B), as Compared with Placebo.

The high dose of bevacizumab was 10 mg per kilogram of body weight. The low dose of bevacizumab was 3 mg per kilogram. Doses were given every two weeks. P values were calculated by the log-rank test.
Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial

Bernard Escudier, Anna Pluzanska, Piotr Koralewski, Alain Ravaud, Sergio Bracarda, Cezary Szczylik, Christine Chevreau, Marek Filipek, Bohuslav Melichar, Emilio Bojetta, Vera Gorbunova, Jacques-Olivier Bay, Istvan Bodrogi, Agnieszka Jagiello-Gruszfeld, Nicola Moore, for the AVOREN Trial investigators

Escudier B, Lancet 2007
Figure 2: Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival
Interim analysis of overall survival based on 251 of 450 scheduled events. Median overall survival had not been reached in the bevacizumab plus interferon alfa group. Final analysis of progression-free survival based on 505 progression events.
Bevacizumab: Phase 3 Trials in Renal Cell Carcinoma

Patient Population: Metastatic Clear Cell Ca No Prior Systemic Therapy

CALGB 90206
N = 732

IFNα 9.0 MU TIW

IFNα 9.0 MU TIW + Bevacizumab 10 mg/kg d1,15

BO17705 (Avoren)
N = 649

IFNα 9.0 MU TIW + Bevacizumab 10 mg/kg d1,15

IFNα 9.0 MU TIW + Placebo

<table>
<thead>
<tr>
<th>CALGB 90206¹</th>
<th>AVOREN²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>IFNα</td>
</tr>
<tr>
<td>ORR</td>
<td>13.1%</td>
</tr>
<tr>
<td>PFS (med)</td>
<td>5.2 mos</td>
</tr>
</tbody>
</table>

¹ Rini, B: GU Malignancy Symposium, ASCO 2/08; ² Escudier, B et al: The Lancet, 2007

Bukowski RM, Berlin 2008
Bevacizumab: conclusions

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>Setting</th>
<th>Pts</th>
<th>PFS (months)</th>
<th>OR (%)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escudier</td>
<td>Bevacizumab + IFN</td>
<td>1st line</td>
<td>649</td>
<td>10.2 vs 5.4 (p&lt;0.0001)</td>
<td>31 vs 13 (p&lt;0.0001)</td>
<td>HR: 0.75 (p&lt;0.0026)</td>
</tr>
<tr>
<td>(Lancet, 2007)</td>
<td>vs placebo + IFN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Bevacizumab + interferon has demonstrated improvements in PFS compared to interferon + placebo
- Bevacizumab + interferon can be considered an alternative treatment for the first-line therapy of mRCC
Inhibitors of mTOR

Rini BI, ASCO 2008
Temsrirolimus
Randomized Phase II Study of Multiple Dose Levels of CCI-779, a Novel Mammalian Target of Rapamycin Kinase Inhibitor, in Patients With Advanced Refractory Renal Cell Carcinoma


Table 3. Tumor Response Rates of RCC Patients Treated With CCI-779

<table>
<thead>
<tr>
<th>Response</th>
<th>CCI-779 Dose Level</th>
<th>25 mg (n = 36)</th>
<th>75 mg (n = 38)</th>
<th>250 mg (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 111)</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td>1</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td>7</td>
<td>6.3</td>
<td>2</td>
</tr>
<tr>
<td>CR/PR</td>
<td></td>
<td>8</td>
<td>7.2</td>
<td>2</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>3.2 to 13.7</td>
<td>0.7 to 18.7</td>
<td>1.7 to 21.4</td>
</tr>
<tr>
<td>MR†</td>
<td></td>
<td>29</td>
<td>26.1</td>
<td>5</td>
</tr>
<tr>
<td>SD ≥ 8 weeks, &lt; 24 weeks</td>
<td>23</td>
<td>20.7</td>
<td>8</td>
<td>22.2</td>
</tr>
<tr>
<td>SD ≥ 24 weeks</td>
<td>19</td>
<td>17.1</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>CR/PR/MR/SD ≥ 24 weeks</td>
<td>56</td>
<td>50.5</td>
<td>19</td>
<td>52.8</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>40.8 to 60.1</td>
<td>35.5 to 69.6</td>
<td>38.3 to 71.4</td>
</tr>
<tr>
<td>PD</td>
<td></td>
<td>22</td>
<td>19.8</td>
<td>6</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>10</td>
<td>9.0</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 7. Classification of RCC Patients Treated With CCI-779 Into Risk Groups for Survival

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Total (n = 111)</th>
<th>25 mg (n = 36)</th>
<th>75 mg (n = 38)</th>
<th>250 mg (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Good</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>48</td>
<td>43</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td>Poor</td>
<td>49</td>
<td>44</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>Unknown*</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: RCC, renal cell carcinoma.
*Patients had data missing for one or more of the prognostic factors and could not be assigned to a risk group.

Table 8. Median Survivals of CCI-779-Treated RCC Patients by Risk Group

<table>
<thead>
<tr>
<th>CCI-779 Dose Level</th>
<th>Good</th>
<th></th>
<th></th>
<th>Intermediate</th>
<th></th>
<th></th>
<th></th>
<th>Poor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>Median Survival (months)</td>
<td>95% CI</td>
<td>No.</td>
<td>%</td>
<td>Median Survival (months)</td>
<td>95% CI</td>
<td>No.</td>
</tr>
<tr>
<td>25 mg (n = 36)</td>
<td>2</td>
<td>6</td>
<td>18.4</td>
<td>18.4 to 23.6</td>
<td>14</td>
<td>39</td>
<td>23.0</td>
<td>12.5 to NA</td>
<td>20</td>
</tr>
<tr>
<td>75 mg (n = 35)*</td>
<td>2</td>
<td>6</td>
<td>NA</td>
<td>24.1 to NA</td>
<td>14</td>
<td>40</td>
<td>20.9</td>
<td>10.4 to 26.1</td>
<td>19</td>
</tr>
<tr>
<td>250 mg (n = 34)*</td>
<td>4</td>
<td>12</td>
<td>22.4</td>
<td>14.4 to NA</td>
<td>20</td>
<td>59</td>
<td>19.3</td>
<td>18.5 to 29.5</td>
<td>10</td>
</tr>
<tr>
<td>All (n = 105)</td>
<td>8</td>
<td>8</td>
<td>23.8</td>
<td>17.7 to 27.1</td>
<td>48</td>
<td>46</td>
<td>22.5</td>
<td>16.9 to 25.7</td>
<td>49</td>
</tr>
</tbody>
</table>

Abbreviations: RCC, renal cell carcinoma; NA, not available.
*Three patients had data missing for one or more of the prognostic factors and could not be assigned a risk group.
Temsirilimus: Phase III trial for first-line therapy of poor-risk RCC

Advanced RCC
No prior therapy
KPS ≥60 (N=626)

- IFN-α (18 million U three times per week)
- Temsirolimus (25 mg weekly)
- Temsirolimus & IFN-α (15 mg weekly; 6 MU twk)

- **Primary end point**: Overall Survival
- **Demographics**
  - MSKCC **poor-risk patients** (modified criteria)
  - Predominately clear-cell carcinoma
Poor-risk patients

- At least three of the following six predictors of short survival were required:
  
  - **LDH** > 1.5 times the upper limit of the normal range
  - **Hemoglobin** level below the lower limit of the normal range
  - **Calcium** level > 10 mg per deciliter
  - **Time from initial diagnosis** of renal-cell carcinoma to randomization < 1 year
  - **Karnofsky performance score** of 60 or 70
  - **Metastases** in multiple organs
Temsirolimus vs IFN
OS: 10.9 vs 7.3 months
HR: 0.73; p=0.008

Temsirolimus vs IFN
PFS: 3.8 vs 1.9 months
p<0.001
**Temsirrolimus: conclusions**

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>Setting</th>
<th>Pts</th>
<th>PFS (months)</th>
<th>OR (%)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudes (NEJM, 2007)</td>
<td>Temsirolimus vs IFN vs TEMSR+IFN</td>
<td>1st line, poor-risk</td>
<td>626</td>
<td>3.7 vs 1.9 vs 3.7</td>
<td>9 vs 7 vs 11</td>
<td>HR: 0.73 (p=0.0069)</td>
</tr>
</tbody>
</table>

- Temsirolimus as a single agent (25 mg iv weekly) significantly improves outcomes as first-line therapy of poor-risk mRCC patients
- The combination of temsirolimus + IFN-α did not significantly improve survival vs IFN-α

* No statistically significant according to O'Brien-Fleming
Everolimus
Everolimus: phase 2 trial

- Everolimus is an oral mTOR inhibitor
- Promising anti-tumor activity in patients with pretreated RCC:
  - response rate 32%
  - stable disease 51%

Jac J, ASCO 2007
Everolimus: Phase III Trial for advanced RCC patients pretreated with inhibitors of VEGFR

Motzer R, ASCO 2008
Progression-Free Survival by Treatment
Central Radiology Review

Hazard ratio = 0.30
95% CI [0.22, 0.40]

Median PFS
Everolimus: 4.0 mo
Placebo: 1.9 mo

Log rank P value < 0.001

Patients at Risk
Everolimus | Placebo
272       | 138
132       | 32
47        | 4
8         | 1
2         | 0
0         | 0
0         | 0

Motzer R, ASCO 2008
Everolimus: conclusions

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>Setting</th>
<th>Pts</th>
<th>PFS (months)</th>
<th>OR (%)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzer (Lancet, 2008)</td>
<td>Everolimus vs placebo</td>
<td>2nd line</td>
<td>410</td>
<td>4.0 vs 1.9 (p&lt;0.001)</td>
<td>1 vs 0</td>
<td>HR: 0.83 (p=0.23)</td>
</tr>
</tbody>
</table>

- Everolimus is the first and only agent with established clinical benefit for the treatment of patients with advanced renal cancer after therapy with inhibitors of VEGF receptors.
### RCC Therapeutic algorithm: 2008

<table>
<thead>
<tr>
<th>Patients</th>
<th>Setting</th>
<th>Therapy (level 1)</th>
<th>Options (level ≥2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>MSK Risk: good or intermediate</td>
<td><strong>Sunitinib</strong> or <strong>Bevacizumab + IFN</strong></td>
<td>HD IL-2 Clinical Trials Observation</td>
</tr>
<tr>
<td></td>
<td>MSK Risk: poor</td>
<td><strong>Temsirolimus</strong></td>
<td>Sunitinib Clinical trials</td>
</tr>
<tr>
<td>Refractory</td>
<td>Cytokine refractory</td>
<td><strong>Sorafenib</strong></td>
<td>Sunitinib Bevacizumab</td>
</tr>
<tr>
<td></td>
<td>Refractory to angiogenesis inhibitors</td>
<td><strong>Everolimus</strong> Clinical Trials</td>
<td>Investigational</td>
</tr>
</tbody>
</table>
The present….:
an embarrassment of riches?
Targeted therapies: challenges and future directions

- Combination therapy
- New schedules
- Sequential strategies
- Role of cytokines
- New agents
- Predictive biomarkers
- Adjuvant and neo-adjuvant therapy
Ongoing studies…
Phase III Study of Bevacizumab plus Temsirolimus vs Bevacizumab plus IFN for First-line Treatment of mRCC

Eligibility criteria
- Metastatic RCC
- No prior systemic treatment
- No brain metastases

Primary end-point: PFS
Randomised Phase III Study of Temsirolimus vs Sorafenib as second-line Therapy in mRCC

Eligibility criteria
- Metastatic clear cell RCC
- Measurable disease
- Failed sunitinib
- Karnofsky PS ≥70%
- ≥1 measurable lesion by RECIST
- No prior mTOR inhibitors
- No brain metastases

Primary end-point: PFS

NCT00474786. www.clinicaltrials.gov
**START: Randomised Phase II Sequential Two-agent Assessment in RCC Therapy**

**Eligibility criteria**
- mRCC of any type
- PS 0/1
- No brain mets
- No prior systemic therapy

**Objectives:**
- Estimate TTP1 and ORR with each drug (first-line setting)
- Estimate TTP2 and ORR with each drug (second-line setting)
- Estimate and rank TTP1 + TTP2 for each sequence

**Stratification:**
- Clear cell vs non-clear cell
- Prior nephrectomy (yes/no)
- PS (0/1)
S-TRAC:
Sunitinib Phase III Trial in Adjuvant Renal Cancer

High-risk patients according to UISS Staging System*
N=236

- Endpoint:
  Disease-free survival

Nephrectomy → Stratify → Randomise

Sunitinib 50 mg/day 4 weeks on/2 weeks off for 1 year
Placebo for 1 year

Primary end point: Disease-free survival
Secondary end points: OS, safety, patient-related outcomes, association of molecular markers with regression-free survival

*T3 N0 or NX, M0, Fuhrman’s grade ≥2, ECOG ≥1 or T4 N0 or NX, M0, any Fuhrman’s grade, and any ECOG status or Any T, N1-2, M0, any Fuhrman’s grade, and any ECOG status

Start Date: September 2007; recruiting
NCT00375674. www.clinicaltrials.gov
ASSURE:
Adjuvant Sorafenib or Sunitinib for Unfavourable RCC

ECOG-sponsored, randomised, double-blind, multicentre phase III trial; currently recruiting

Non-metastatic RCC
Disease stage II–IV
N=1332

Stratify*

Sunitinib 50 mg/day
4 weeks on/2 weeks off
Total = 9 cycles†

Sorafenib 400 mg
twice daily for 6 weeks
Total = 9 cycles†

Placebo twice daily
for 6 weeks
Total = 9 cycles†

• Duration: 1 year
• Primary endpoint: DFS

*UISS (II–V); Histologic subtype clear cell/non-clear cell
†Biopsy at recurrence

Start Date: May 2006; recruiting

NCT00326898. www.clinicaltrials.gov
SORCE: Sorafenib in Patients with Resected Primary RCC at High or Intermediate Risk of Relapse

Patients with high- and intermediate- risk resected RCC

N=1420

Nephrectomy

Stratify

Randomisation

Sorafenib 400 mg b.i.d. for 3 years

Sorafenib 400 mg b.i.d. for 1 year then placebo for 2 years

Placebo for 3 years

Endpoint: time to metastases

Duration: 1 vs 3 years

Start Date: June 2007; recruiting

In the next years....

• Ongoing studies will clarify:

  – The role of combination therapy (also including cytokines…)
  – The optimal sequence of therapy
  – Therapy for resistant disease
  – Long term toxicities...
  – Molecular biomarkers defining groups benefiting from anti-VEGF therapy