Sorafenib for renal cell carcinoma

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Renal Cell Carcinoma: Drugs and Targets

pVHL = HIF\(\alpha\) → CCI-779

Bevacizumab → VEGF

KDR → PDGF

PDGFR

TGF\(\alpha\)

EGFR → Erlotinib

Sunitinib, sorafenib

Sunitinib, sorafenib
Sorafenib (Nexavar®) 
A Novel, Orally-Active Multi-Kinase Inhibitor

Approved in the US in Dec 2005 for advanced RCC

*In vitro* inhibitor of C-Raf, wild-type B-Raf, *b-raf* V600E, VEGFR -1/-2/-3, PDGFR-β, c-Kit, and Flt-3

Broad-spectrum anti-tumour activity and inhibition of angiogenesis in several tumour xenografts

Sorafenib prevented tumour growth in RCC VHL⁻/⁻ xenografts, via inhibition of angiogenesis²

Sorafenib: phase II and III studies

Based on phase I data, continuous oral dosing of sorafenib 400mg twice daily (b.i.d.) was selected for further evaluation in patients with advanced RCC

Sorafenib phase II and III clinical trials:

- phase II Randomised Discontinuation Trial (RDT)
- phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs)
- randomised phase II trial of sorafenib versus IFN (first-line)
- phase II trial in Japanese patients
**Phase II RDT: study design**

Response assessment (change from baseline in bidimensional tumour measurements)

- **Sorafenib 400mg b.i.d. 12-week run-in**
  - Tumour shrinkage ≥25%
  - Tumour growth/shrinkage <25%
  - Tumour growth ≥25%

  - Sorafenib 400mg b.i.d. open-label
  - Sorafenib 400mg b.i.d. 12 weeks
  - Placebo 12 weeks
  - Off study

Progression-free at 24 weeks (%)

*Patients who progressed on placebo could cross over to sorafenib*
Phase II RDT: sorafenib significantly delayed progression compared with placebo

At 24 weeks, 50% of patients with advanced RCC remained progression free in the sorafenib group compared with 18% in the placebo group (p=0.0077)

SORAFENIB improves PFS over placebo in 2nd line setting

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~905

Stratification
• Motzer criteria
• Country

Sorafenib 400 mg bid

Major endpoints
• Survival (alpha=0.04)
• PFS (alpha=0.01)

Placebo

Escudier et al, NEJM 2007
TARGETs Progression-Free Survival Benefit*

Median PFS
- Sorafenib = 24 weeks
- Placebo = 12 weeks
Hazard ratio (S/P) = 0.51

*Based on investigator assessment
TARGET: Final OS Analysis
16 Months Post-Crossover: Intent-to-Treat

Sorafenib (n=451) = 17.8 months
Placebo (n=452) = 15.2 months
HR (sorafenib/placebo) = 0.88
95% CI: 0.74–1.04
P=0.146*

Bukowski et al, ASCO 2007

*Non-significant; O’Brien–Fleming threshold for statistical significance α=0.037
TARGET: Pre-planned Secondary Analysis

OS Data for Placebo Patients Censored*

- Sorafenib (n=451) = 17.8 months
- Placebo (n=452) = 14.3 months

HR (sorafenib/placebo) = 0.78
95% CI: 0.62–0.97
P=0.0287**

*Censored at 30 June 2005, approx. start of crossover

**Statistically significant: O’Brien–Fleming threshold for statistical significance \( \alpha = 0.037 \)

Bukowski et al, ASCO 2007
TARGETs: sorafenib has a predictable and manageable side-effect profile

<table>
<thead>
<tr>
<th>Incidence of adverse events* (%)</th>
<th>Sorafenib (n=451)</th>
<th>Placebo (n=451)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grades 3–4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Decreased haemoglobin</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Bone pain</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Tumour pain</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

*National Cancer Institute-Common Toxicity Criteria (Version 3); adverse events occurring in ≥2% of patients
†One patient was not evaluable for safety

Sorafenib induces changes in vascularization
Imaging techniques can show these changes

before

after 3W

PR

GR

M. Lamuraglia et al. ECCO 2005
Changes in tumor vascularization predict OS

Lamuraglia et al, Eur J Cancer, 2006
But sorafenib is not as active as expected in first line

Randomized phase II trial of first-line treatment with sorafenib vs interferon in patients with advanced renal cell carcinoma: final results

Cezary Szczylík, Tomasz Demkow, Michael Staehler, Frédéric Rolland, Sylvie Negrier, Thomas E Hutson, Ronald M Bukowski, Urban J Scheuring, Konrad Burk, Bernard Escudier

ASCO 2007, abstract 5025
Study 11848: Design
First-line sorafenib versus IFN: randomized phase II trial

ELIGIBILITY CRITERIA
- Unresectable RCC ± metastases
- Clear cell histology
- Measurable disease
- No prior systemic therapy
- ECOG Performance Status 0 or 1
- Good organ function
- No brain metastases
- All MSKCC risk groups

Period 1
Sorafenib 400mg bid (n=97)
Stratification by MSKCC
Open-label randomization 1:1
IFN 9 MIU t.i.w. (n=92)

Period 2
Sorafenib 600mg bid (n=44)

PROGRESSION

Primary objective
Period 1: PFS sorafenib vs IFN
29 Sept 2006: 121 PFS events

Period 2: PFS and clinical benefit
31 Dec 2006

Secondary objective
Disease Control Rate (DCR); Quality of Life (QoL); best response rate; duration of response; overall survival (OS)
Progression-Free Survival: Period 1

Median PFS
Sorafenib = 5.7 months
IFN = 5.6 months
HR (IFN/sorafenib) = 0.88 (95% CI: 0.61–1.27)
p=0.504 (log-rank test)
Results: period 2
IFN → sorafenib 400mg bid **versus** sorafenib 400mg bid → 600mg bid

**ELIGIBILITY CRITERIA**
- Unresectable RCC ± metastases
- Clear cell histology
- Measurable disease
- No prior systemic therapy
- ECOG Performance Status 0 or 1
- Good organ function
- No brain metastases
- All MSKCC risk groups

**Period 1**
- Sorafenib 400mg orally bid (n=97)
- IFN 9 MIU t.i.w. (n=92)

**Period 2**
- Sorafenib 600mg bid (SOR400→600)
- Sorafenib 400mg bid (IFN→SOR400)

**PROGRESSION**

**Objectives:**
- Is dose escalation useful?
- Does IFN → sorafenib switch mimic TARGET data?
## Progression-Free Survival: Period 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total with PFS event, n</th>
<th>Median PFS (K–M) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOR400→600, N=44</td>
<td>25</td>
<td>4.1 months (1.9–5.3)</td>
</tr>
<tr>
<td>IFN→SOR400, N=51</td>
<td>28</td>
<td>5.5 months (3.7–7.1)</td>
</tr>
</tbody>
</table>

*Investigator assessed; 31 December 2006 cut-off*
But dose of sorafenib might be too low?

A Phase II Trial of Intra-Patient Dose-Escalated-Sorafenib in Patients with Metastatic Renal Cell Cancer

R. Amato, P. Harris, M. Dalton, M. Khan, J. Zhai, J. Brady, J. Jac, R. Alter, R. Hauke, S. Srinivas

ASCO 2007, abstract 5026
Dose Escalated Sorafenib for Renal Cell Carcinoma: Phase 2 Study

Treatment regimen:
- 400 mg bid daily oral therapy day 1-28;
- 600 mg bid day 29-56;
- 800 mg bid day 57 throughout

Dose modification for grade 3/4 toxicity

Monitoring of CBC, chemistry, and amylase/lipase

Response assessed by RECIST every 8 weeks

Treatment continued unless progression or intolerability
At 800 mg dose level
  5 patients had dose held between weeks 2 through 4
  3 patients were dose reduced

Doses were escalated to 1200 mg in 41 of 44 patients

Doses were escalated to 1600 mg in 32 of 41 patients

**SUMMARY**

- 41 patients were able to receive 1200 or 1600 mgs per day of Sorafenib
- 3 patients were unable to be dose escalated
- Those with early toxicity have difficulty with dose escalation
# Dose Escalated Sorafenib for Renal Cell Carcinoma

## Results: Best Response by RECIST

<table>
<thead>
<tr>
<th>Best Response</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Partial Response</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>Stable Disease ≥ 6 months</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Progression defined as ≤ 4 months</td>
<td>11</td>
<td>25</td>
</tr>
</tbody>
</table>
And dose of TKIs might be an issue:
Probability of PR or CR in mRCC Increased with Mean Daily Sunitinib Exposure
Houk et al, ASCO 2007, abstract 5027

![Graph showing the relationship between AUCss sunitinib (ug•hr/mL) and Probability of a response. The probability increases with increasing AUCss, and the P-value for AUC is 0.023.](image-url)
QUESTIONS

1. Benefit of combination?

2. Benefit of sequential treatment?

3. Rôle of sorafenib?
QUESTIONS

1. Benefit of combination?

2. Benefit of sequential treatment?

3. Rôle of sorafenib?
Sorafenib plus bevacizumab: phase I/II study design

ELIGIBILITY CRITERIA
- Advanced RCC
- All histological sub-types
- ECOG PS 0–1
- Prior therapy allowed
  - No VEGF, VEGFR2 or MAP kinase pathways inhibitors
- Prior nephrectomy not required
- No CNS disease
- No active vascular disease (CNS or cardiac) within six months

Phase I

Week 1 2 3 4 5 6 7 8 9

Progression

B B B B B Re-evaluate

Sorafenib

Dose escalate until MTD (maximum-tolerated dose)

CR PR SD

Continue treatment until tumour progression

Progression

Off

Phase II

Adapted from: Sosman JA, et al. ASCO 2006; Atlanta, GA, USA

VEGFR = VEGF receptor; MAP = mitogen-activated protein
CNS = central nervous system; CR = complete response
PR = partial response; SD = stable disease; B = bevacizumab
Sorafenib plus bevacizumab: phase I/II tumour responses

Change in tumour measurements (%)

-90  -60  -30   0    30

Stable disease
Response

- sor = sorafenib
- q.d. = once daily; vitB₆ = vitamin B₆

Adapted from: Sosman JA, et al. ASCO 2006; Atlanta, GA, USA
QUESTIONS

1. Benefit of combination?

2. Benefit of sequential treatment?

3. Rôle of sorafenib?
Sequential use of sorafenib and sunitinib: retrospective analysis in 90 patients

MP Sablin (1), L Bouaita (1), C Balleyguier (1), J Gautier (2), C Celier (3), S Oudard (4), A Ravaud (3), S Negrier (2), B Escudier (1)

(1) Institut Gustave Roussy, Villejuif, France
(2) Centre Léon Bérard, Lyon, France
(3) Hôpital Saint-André, Bordeaux, France
(4) Hôpital Européen Georges Pompidou, Paris, France

ASCO 2007
### Table 4: Efficacy of Su after So

<table>
<thead>
<tr>
<th>So</th>
<th>PR no. (%)</th>
<th>SD no. (%)</th>
<th>PD no. (%)</th>
<th>NE no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR no.</td>
<td>11</td>
<td>2 (18)</td>
<td>7 (64)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>SD no.</td>
<td>45</td>
<td>6 (13)</td>
<td>24 (53)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>PD no.</td>
<td>10</td>
<td>2 (20)</td>
<td>3 (30)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>NE no.</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Su</td>
<td>So</td>
<td>PR no.(%)</td>
<td>SD no.(%)</td>
<td>PD no.(%)</td>
</tr>
<tr>
<td>------</td>
<td>----</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>PR</td>
<td>5</td>
<td>1 (20)</td>
<td>2 (40)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>SD</td>
<td>12</td>
<td>1 (8)</td>
<td>7 (58)</td>
<td>4 (34)</td>
</tr>
<tr>
<td>PD</td>
<td>5</td>
<td>0</td>
<td>3 (60)</td>
<td>2 (40)</td>
</tr>
</tbody>
</table>
Conclusions

The sequential administration of sorafenib and sunitinib is beneficial even if these two drugs share the same targets.

The use of sorafenib followed by sunitinib seems to be superior with:
- a better median survival (not reached vs 70 weeks)
- better PFS for each arm.
- the obtention of partial responses after a progression with sorafenib (20%).
QUESTIONS

1. Benefit of combination?

2. Benefit of sequential treatment?

3. Role of sorafenib?
Sorafenib should be used

- as first choice therapy in patients who failed cytokines
- in first line, as a good alternative to interferon
- after sunitinib
- activity of sorafenib should continue to be explored:
  1. in combination with other agents (bevacizumab, temsirolimus, interferon.....)
  2. at higher dose, to confirm Amato’s data on dose escalation