Sunitinib Continuous 37.5 mg/Day Dosing in Cytokine-Refractory Metastatic RCC

Presentation discussed in this issue:


---

Slides from the journal article

**Phase II Study of Sunitinib Administered in a Continuous Once-Daily Dosing Regimen in Patients With Cytokine-Refractory Metastatic Renal Cell Carcinoma**

**Escudier B et al.**

Sunitinib: Mechanism of Action

Inactivation of the VHL tumor suppressor gene occurs in at least 60 percent of clear cell renal cell carcinomas, and this results in increased transcription of HIF-regulated genes such as VEGF and PDGFβ that play a role in promoting angiogenesis.

Sunitinib interacts with the intracellular kinase domains of tyrosine kinase receptors such as VEGFR and PDGFR in vitro and inhibits their signalling. Other sunitinib molecular targets include KIT, FLT-3, CSF-1R and RET.


---

Introduction

- A Phase III study of first-line sunitinib 50 mg/d (4 weeks on/2 weeks off) in metastatic RCC (mRCC) demonstrated improvements in ORR, PFS, OS compared to IFN-alpha (*J Clin Oncol* 2009;27:3584).

  - Overall response rates (ORR): 42%
  - Median progression free survival (PFS): 8.2 mos
  - Median overall survival (OS): 23.9 mos

- An alternative continuous dosing regimen of sunitinib may provide added treatment flexibility and lessen the incidence or severity of adverse events.
  - Evening (PM) rather than morning (AM) administration may reduce drug-related fatigue or nausea.

- **Current study objectives (N = 107):**
  - Assess the efficacy and tolerability of continuous sunitinib at a starting dose of 37.5 mg/d administered in the AM or PM in patients with cytokine-refractory mRCC.

Phase II, Open-Label, Randomized Study of Continuous Once-Daily Sunitinib in Patients with mRCC

Eligibility
Histologically-proven mRCC and measurable disease
Failure of one prior cytokine therapy

Morning Administration*
Sunitinib starting dose of 37.5 mg/d (n = 54)

Evening Administration*
Sunitinib starting dose of 37.5 mg/d (n = 53)

Patients receiving at least one dose of sunitinib underwent combined efficacy and safety analyses

* Individual dosage titrated within range of 25 mg/d to 50 mg/d based on study-defined tolerability criteria

Overall Combined (AM and PM Administration) Efficacy Results (N = 107)

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (PR*)</td>
<td>20%</td>
</tr>
<tr>
<td>Duration of response (DoR)</td>
<td>7.2 mos</td>
</tr>
<tr>
<td>Clinical benefit rate (CBR) (PR + stable disease &gt; 6 months)</td>
<td>53%</td>
</tr>
<tr>
<td>Median progression-free survival (PFS)</td>
<td>8.2 mos</td>
</tr>
<tr>
<td>Median overall survival (OS)</td>
<td>19.8 mos</td>
</tr>
</tbody>
</table>

* No patient achieved CR.
**Post-Baseline Tumor Assessment in the Combined Patient Population Receiving At Least One-Dose of Sunitinib**

![Graph showing tumor shrinkage](image)

**Tumor shrinkage was observed in 85% of patients (n=87)**

* Five patients did not have postbaseline assessments.


---

**Most Commonly Reported (Occurring in >10% of Patients) Grade 3 Treatment-Related Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AM Arm (N=54)</th>
<th>PM Arm (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

- Grade 4 AEs reported (6): hematemesis, renal failure, vertigo, dehydration, hyponatremia and hemorrhagic gastritis
- Grade 5 AEs reported (1): acute myeloblastic leukemia

# Tolerability and Health-Related Quality of Life of Continuous Sunitinib

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AM Arm (N=54)</th>
<th>PM Arm (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Reason for treatment discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>31</td>
<td>57</td>
</tr>
<tr>
<td>Adverse events</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Patient group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With dose interruption</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>With dose escalation to 50 mg/d</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>With dose reduction to 25 mg/d</td>
<td>21</td>
<td>39</td>
</tr>
</tbody>
</table>

No differences were observed in health-related quality of life between patients receiving morning versus evening administration of sunitinib.


---

# Summary and Conclusions

- Continuous sunitinib 37.5 mg/d may be an alternative, more flexible dosing regimen than the standard schedule (50 mg/d, 4 weeks on/2 weeks off) for patients with cytokine-refractory mRCC.

- Efficacy, tolerability and health-related quality of life with continuous sunitinib were comparable in the AM and PM dosing arms.

- Efficacy of continuous sunitinib 37.5 mg/d may be less than with the standard 50 mg/d (4/2) although 95% confidence intervals were overlapping (data shown below from combined analysis of phase II studies).
  - ORR = 20% (vs 42%, 50 mg/d 4/2)
  - Median PFS = 8.2 mos (vs 8.2 mos, 50 mg/d 4/2)
  - Median OS = 19.8 mos (vs 23.9 mos, 50 mg/d 4/2)

- The safety profile and pharmacokinetics (data not shown) of continuous sunitinib 37.5 mg/d were similar to those reported with 50 mg/d intermittent (4/2) schedule.

- The ongoing, randomized Phase II Renal EFFECT Trial (NCT00267748) will further evaluate continuous versus intermittent dosing of sunitinib for mRCC.