5 Minute JournalClub

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

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## CME INFORMATION

## OVERVIEW OF ACTIVITY

Advances in the biologic understanding of renal cell cancer and the emergence of clinical trial data with targeted therapeutic agents have resulted in the availability of novel treatment strategies for this challenging disease. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these rapidly evolving data sets. To bridge the gap between research and patient care, this CME activity will deliver a serial review of recent key presentations and publications and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with renal cell cancer.

## LEARNING OBJECTIVE

- Compare and contrast the efficacy and safety of continuous daily sunitinib with historical data employing a standard intermittent sunitinib treatment approach for patients with cytokine-refractory mRCC.

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Nobody seems to care much anymore about the ancient backbone of medical oncology, cytotoxic chemotherapy, and in the past decade, so-called biologic agents — mainly antibodies, TKIs and other small molecules — have dominated a clinical trials infrastructure that is being led by industry while publicly funded research sputters along.

However, with the many benefits offered by biologics come a panoply of new toxicity issues that challenge clinicians in ways never before imagined. Nowhere is this dynamic more evident than in renal cell cancer in which six new agents have been approved in the past four years.

In this issue of 5MJC, we examine three recent reports that attempt to better define tolerability considerations surrounding the most utilized class of new RCC drugs, the VEGF TKIs. We begin with a **report by Escudier et al** of a Phase II study of continuous daily dosing of sunitinib at 37.5 mg, with findings that look generally similar to the 50-mg four week on, two week off regimen that has become the most commonly used first-line therapy in this disease. Despite this intriguing new data set, no one will stick his or her neck out one way or the other in predicting the results of the hopefully soon to be reported EFFECT trial comparing these two regimens as front-line therapy in a head-to-head Phase II randomized study.

At our recent **renal cell cancer investigator think tank** [login required], Eric Jonasch and others suggested the possibility of yet another sunitinib regimen: 50 mg a day, two weeks on, one week off. The undercurrent to all of these efforts is the belief — variably embraced by RCC investigators — that treatment benefit may in some way be correlated with TKI "dose under the curve." How any of these regimens compares to the recently FDA approved bevacizumab/interferon combination or to bev alone is currently unknown.

Speaking of FDA approval, we also include **two new data sets** on the most recently green-lighted renal cell agent, another TKI, pazopanib, which again, by indirect comparison seems similar to sunitinib. However, Tom Hutson, also on our think tank program, predicts that an upcoming Phase III trial comparing these two complicated TKIs in the first-line setting will demonstrate essentially equivalent efficacy but different side-effect profiles, with pazopanib perhaps better tolerated but bringing with it a significant risk of hepatic dysfunction, usually reversible transaminitis.

The traditional oncology focus on challenging complications of chemotherapy including neutropenic infections, nausea and vomiting has now shifted to an array of new toxicity issues with these novel biologic agents. Our ability to prevent or ameliorate these — either with new dosing and administration schedules or with second- or third-generation agents with different pharmacologic profiles — is important now and could be life-saving in the future, if and when we see imatinib/CML-like magic with these or other similar agents or combinations.

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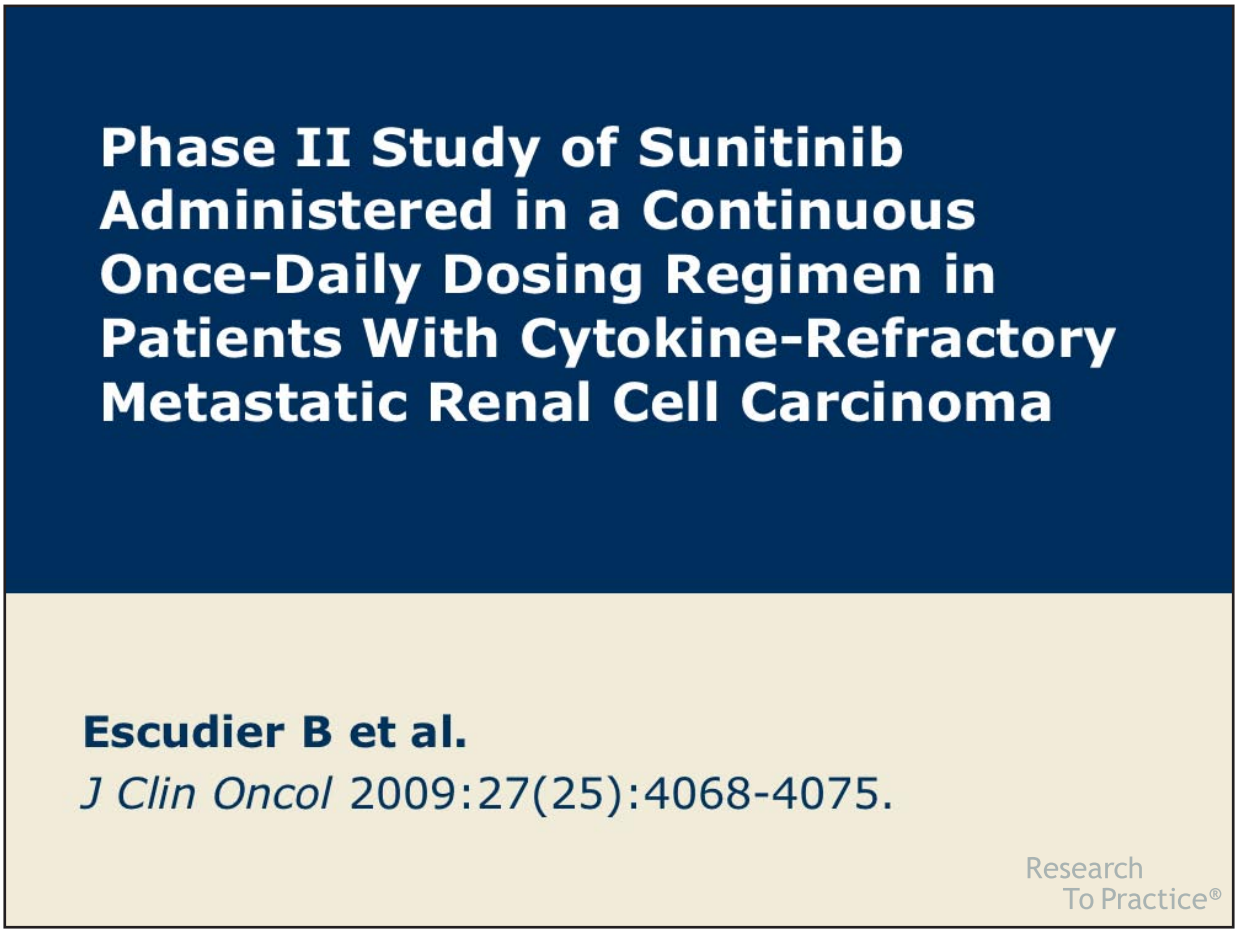
# Sunitinib Continuous 37.5 mg/Day Dosing in Cytokine-Refractory Metastatic RCC

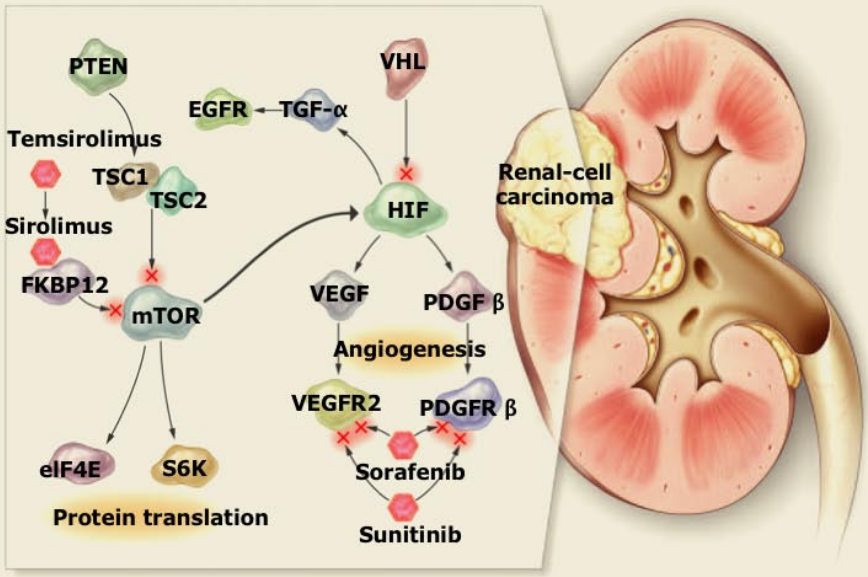
## Presentation discussed in this issue:

Escudier B et al. **Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma.** *J Clin Oncol* 2009;27(25):4068-75. **Abstract**

## Slides from the journal article and transcribed comments from a related interview with Nicholas J Vogelzang, MD below (August 17, 2009)



# 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.

Source: Reprinted with permission. Brugarolas J. *N Engl J Med* 2007:356(2):185-187.

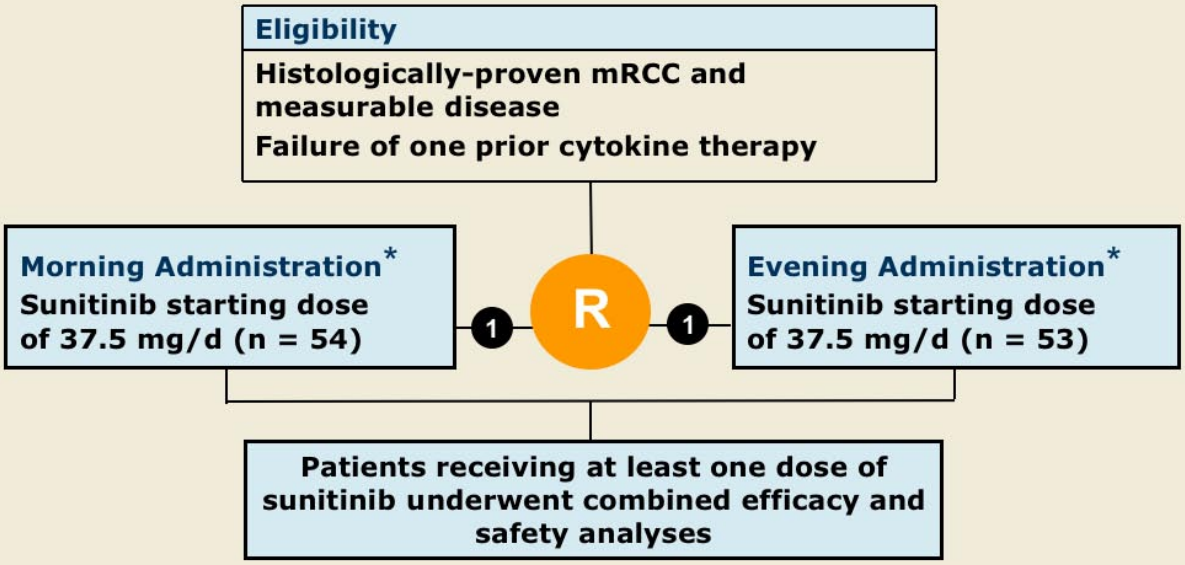


# Introduction

- 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).
- In Phase II studies, standard-dose sunitinib (50 mg/d 4/2 schedule) has demonstrated robust clinical efficacy in cytokine-refractory mRCC (*JAMA* 2006;295:2516, *J Urol* 2007;178:1883, *J Clin Oncol* 2006;24:16):
  - 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.

Source: Escudier et al. *J Clin Oncol* 2009:27(25):4068-75.

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




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

Source: Escudier et al. *J Clin Oncol* 2009:27(25):4068-75.

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

| Clinical Outcome | |
|---|---|
| Overall response rate (PR*) | 20% |
| Duration of response (DoR) | 7.2 mos |
| Clinical benefit rate (CBR) (PR + stable disease > 6 months) | 53% |
| Median progression-free survival (PFS) | 8.2 mos |
| Median overall survival (OS) | 19.8 mos |

* No patient achieved CR.

Source: Escudier et al. *J Clin Oncol* 2009:27(25):4068-75.

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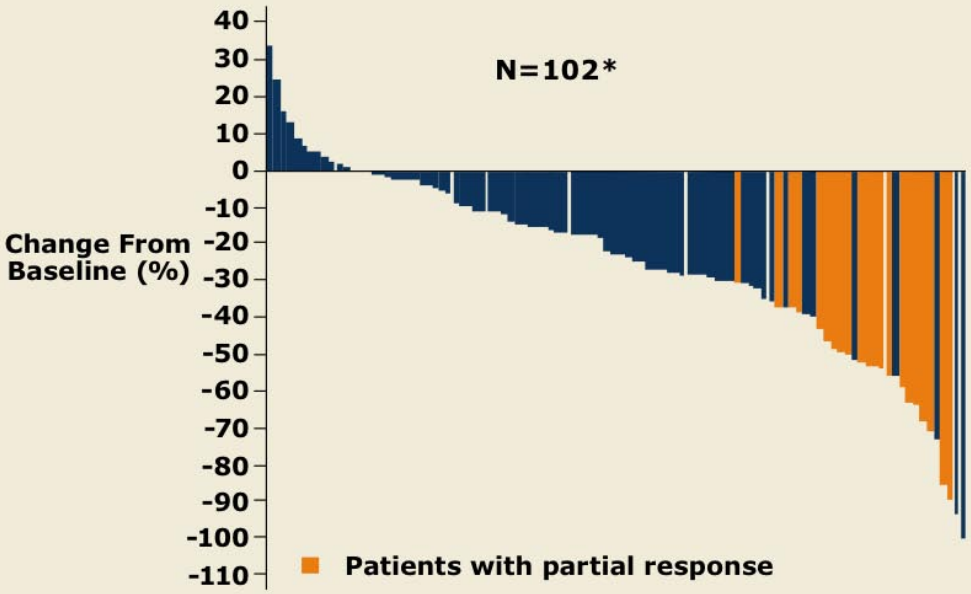
# Post-Baseline Tumor Assessment in the Combined Patient Population Receiving At Least One-Dose of Sunitinib




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

* Five patients did not have postbaseline assessments.

Source: Reprinted with permission. Escudier et al. *J Clin Oncol* 2009:27(25):4068-75.



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

| Adverse Event | AM Arm (N=54) | | PM Arm (N=53) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Hypertension | 6 | 11 | 6 | 11 |
| Asthenia/fatigue | 5 | 9 | 12 | 23 |
| Hand-foot syndrome | 4 | 7 | 6 | 11 |
| Anorexia | 4 | 7 | 5 | 9 |
| Diarrhea | 3 | 6 | 9 | 17 |

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

Source: Escudier et al. *J Clin Oncol* 2009:27(25):4068-75.

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

| Parameter | AM Arm (N=54) | | PM Arm (N=53) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Reason for treatment discontinuation | | | | |
| Disease progression | 31 | 57 | 33 | 62 |
| Adverse events | 7 | 13 | 9 | 17 |
| Patient group | | | | |
| With dose interruption | 35 | 65 | 34 | 64 |
| With dose escalation to 50 mg/d | 15 | 28 | 16 | 30 |
| With dose reduction to 25 mg/d | 21 | 39 | 25 | 47 |

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

Source: Escudier et al. *J Clin Oncol* 2009:27(25):4068-75.

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# 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.

Source: Escudier et al. *J Clin Oncol* 2009:27(25):4068-75.

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**NEIL LOVE, MD:** What are your thoughts about the concept of achieving the optimal benefit with VEGF tyrosine kinase inhibitors by delivering as much of the planned dose as possible?

**NICHOLAS J VOGELZANG, MD:** The available data are not definitive, but we have reported data from a population of patients in whom blood levels of sunitinib were measured. A strong association was observed between the dose delivered and blood levels of sunitinib, which were correlated with response, duration of response and survival.

We also have data from the Phase II study with continuous daily sunitinib that was recently published in the *Journal of Clinical Oncology*. The progression-free survival (PFS) was inferior to the 50-mg four week on, two week off schedule of sunitinib published in *The New England Journal of Medicine*, but the patients in this Phase II study were comprised of a slightly worse prognostic group. So I'm not certain that you can compare apples to oranges.

**DR LOVE:** The median PFS was 8.2 months and overall survival was 19.8 months.

**DR VOGELZANG:** That's correct, and I would point out that this study was conducted between 2005 and 2006, and the only agent available at crossover was sorafenib. We didn't even have the mTOR inhibitors, which I suspect will improve overall survival.

I am eager to see the results of a randomized, Phase II trial (Renal EFFECT Trial), which compares standard sunitinib 50-mg/daily four weeks on, two weeks off to continuous daily dosing of sunitinib 37.5 mg. In evaluating the pharmacokinetic area under the curve, continuous should be as effective as the intermittent schedule.

**DR LOVE:** What was your perception of the side effects with continuous dosing?

**DR VOGELZANG:** I'm a biased investigator. I examine my patients and think, "Hmm. This is going well. I'm pleased with this toxicity parameter." I need to see a direct comparison. In my practice if patients experience excessive toxicity with the 50-mg (four-on, two-off) schedule, then I will automatically drop them to 37.5 mg/day continuous dosing.

**DR LOVE:** Another schedule I've been hearing about is two weeks on, one week off. What are your thoughts about that?

**DR VOGELZANG:** I don't believe that's a good idea. Many strategies exist to ameliorate toxicity. I believe duration of exposure is probably important, and continuously inhibiting the angiogenic signal from the kidney cancer cells to the normal endothelium, which is what sunitinib does, should be important. It should be continuous suppression of angiogenesis.

*Dr Vogelzang is Chair and Medical Director of the Developmental Therapeutics Committee and Co-Chair of the Genitourinary Committee for US Oncology Research via Comprehensive Cancer Centers of Nevada in Las Vegas, Nevada.*