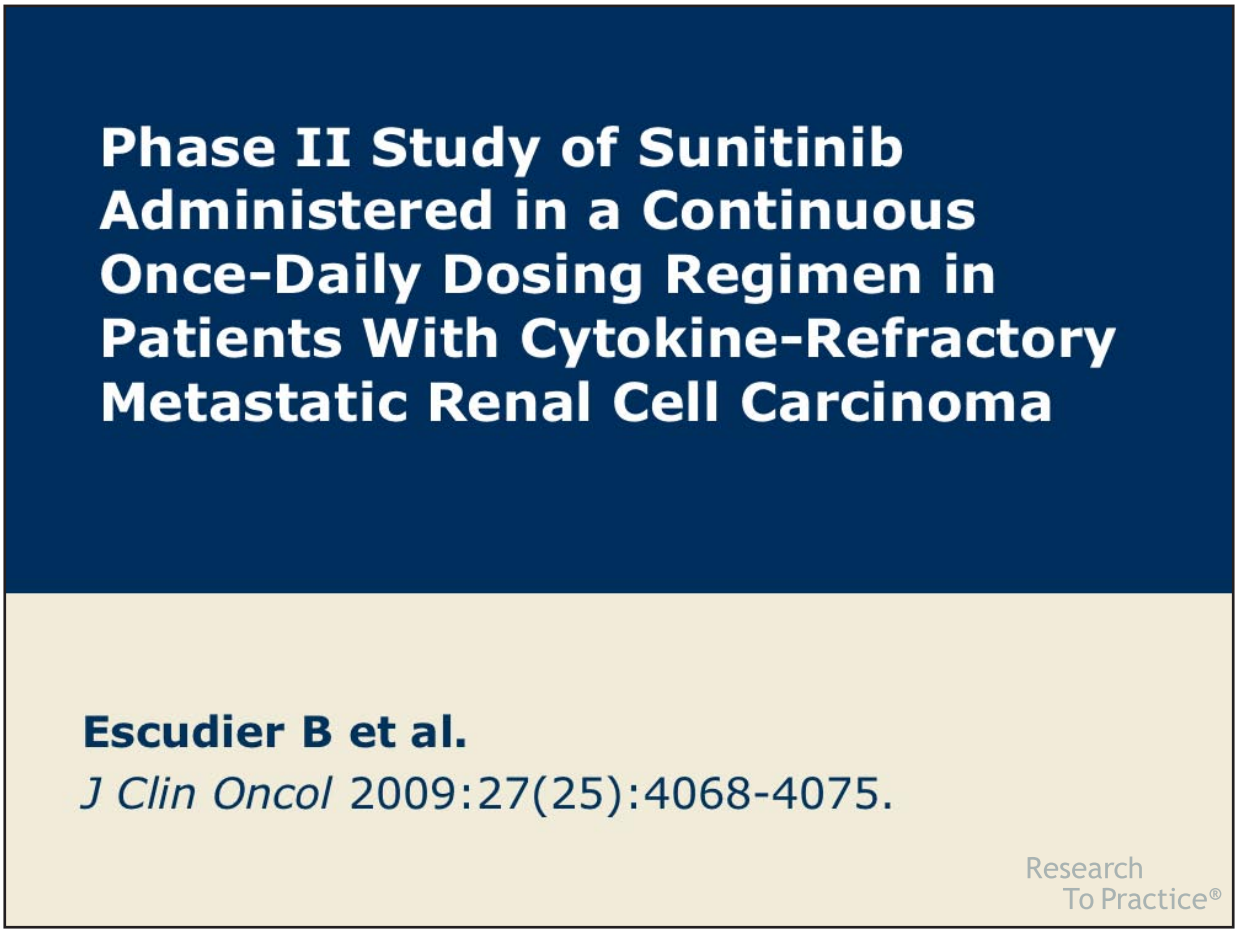
Sunitinib Continuous 37.5 mg/Day Dosing in Cytokine-Refractory Metastatic RCC

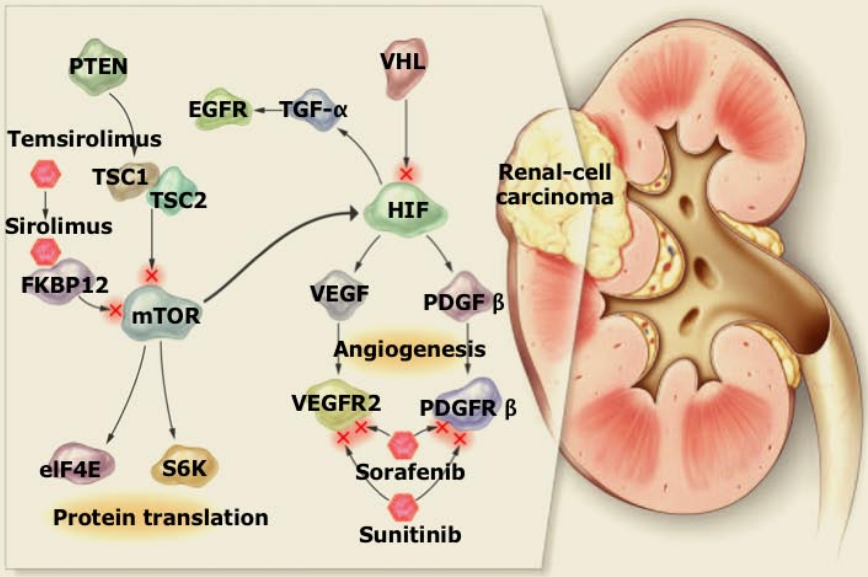
Presentation discussed in this issue:

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



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.

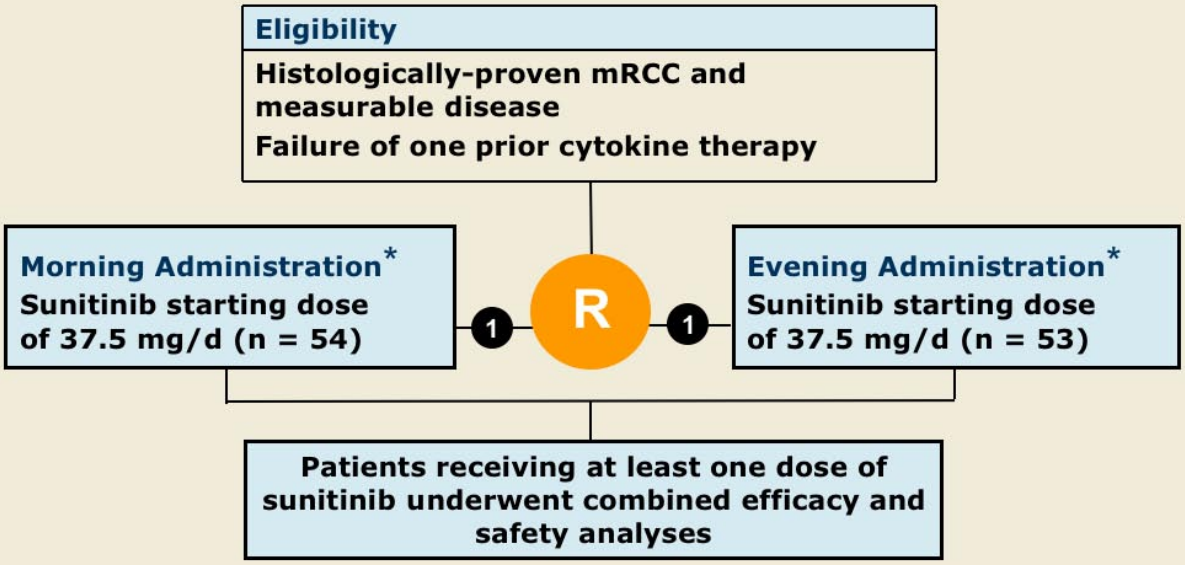
Source: Reprinted with permission. Brugarolas J. *N Engl J Med* 2007:356(2):185-187.

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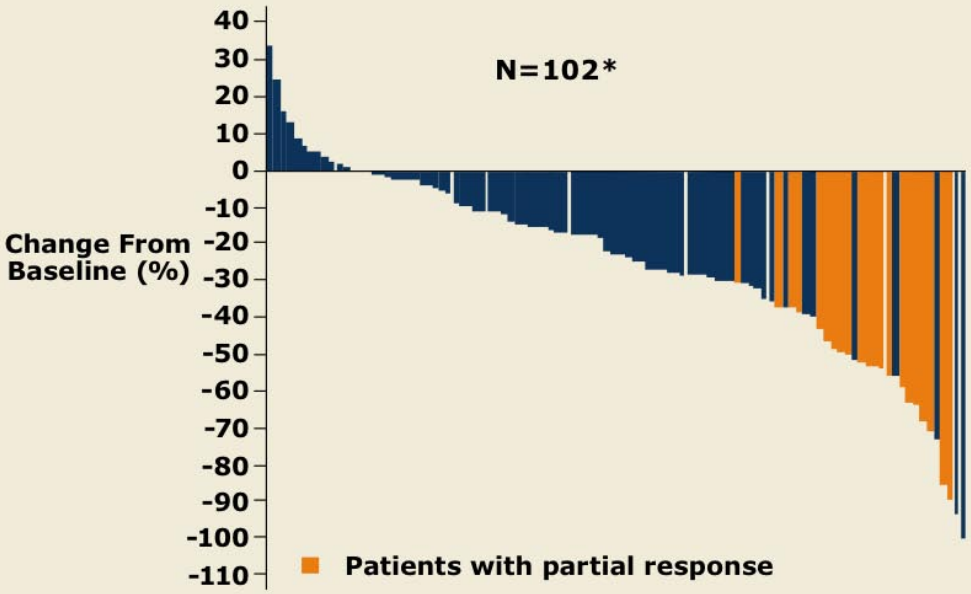
Post-Baseline Tumor Assessment in the Combined Patient Population Receiving At Least One-Dose of Sunitinib



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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