

# Phase II Study of Volociximab (M200), an $\alpha 5\beta 1$ Anti-integrin Antibody in Refractory Metastatic Clear Cell Renal Cell Cancer (RCC)

R. A. Figlin<sup>1</sup>, G. V. Kondagunta<sup>2</sup>, S. Yazji<sup>3</sup>, R. J. Motzer<sup>2</sup>, R. M. Bukowski<sup>4</sup>; <sup>1</sup>UCLA, Los Angeles, CA; <sup>2</sup>Memorial Sloan Kettering Cancer Center, New York, NY; <sup>3</sup>PDL BioPharma, Fremont, CA; <sup>4</sup>Cleveland Clinic Taussig Cancer Center, Cleveland, OH

## ABSTRACT

**Background:** Blocking angiogenesis has been shown to be an effective strategy for controlling tumor growth in RCC. Tumor angiogenesis occurs when pro-angiogenic growth factors are released, stimulating endothelial cell proliferation and migration to form neovessels. M200 is an IgG4 chimeric monoclonal antibody that targets  $\alpha 5\beta 1$ , thereby inducing apoptosis of proliferating endothelial cells. M200 activity is independent of growth factor stimulus, suggesting that binding of fibronectin to  $\alpha 5\beta 1$  occurs downstream of growth factor signaling, and is possibly a final common pathway for the development of neovasculature.

**Methods:** This is a multicenter, open label, single cohort pilot phase II study of 40 patients (pts) with RCC. Pts received no more than 2 prior regimens. Pts received M200 10 mg/kg IV every 2 weeks until disease progression. Pts were evaluated for efficacy every 8 weeks by objective response using RECIST criteria. An independent data safety monitoring board was utilized to review safety data.

**Results:** A total of 40 pts were enrolled. All pts were evaluable for safety and 37 pts for objective response (to date). Median age was 62.8 years. ECOG score was 0 in 27 (67.5%) and 1 in 13 (32.5%) pts. Prior nephrectomy occurred in 39 (97%) pts. Other prior treatment included IL-2 in 15 (37.5%), interferon alpha in 6 (15%), IL-2 + interferon in 2 (5%) pts. Most frequent side effects were fatigue 37.5%, nausea 15% and hypertension 7.5%. Five pts died in the study, four with progressive disease (PD) and 1 with arrhythmia (unrelated to M200). SD was observed in 32/37 (87%) of pts. No changes in hematological, renal and hepatic parameters were noted. Median time to progression was 113+ days. The average peak and trough concentrations of circulating M200 following 6 weeks of treatment were 390  $\mu\text{g/mL}$  and 140  $\mu\text{g/mL}$ , respectively. There were no detectable immune responses to M200.

**Conclusions:** M200 is well tolerated at 10 mg/kg q2w. Stable disease is noted in 87% of pts. Follow-up continues. A higher dose level is being evaluated.

Note: Poster data updated as of April 10, 2006.

## INTRODUCTION

- Volociximab is a high-affinity chimeric (82% human/18% murine) IgG4 monoclonal antibody that specifically binds  $\alpha 5\beta 1$  integrin.
- Volociximab is being developed as an anti-angiogenic agent targeting  $\alpha 5\beta 1$  integrin for the treatment of solid tumors.
- Volociximab binds to  $\alpha 5\beta 1$  integrin and blocks the ligation of  $\alpha 5\beta 1$  to fibronectin. This ligation is critical for the survival of proliferating endothelial cells.
- This mechanism of action is different from other angiogenesis inhibitors currently approved or in clinical trials, which primarily focus on inhibiting the vascular endothelial growth factor (VEGF) pathway.
- Volociximab acts downstream of the growth factors (VEGF and bFGF) that stimulate angiogenesis. By inhibiting  $\alpha 5\beta 1$  integrin, volociximab may inhibit tumor angiogenesis, and may arrest or prevent tumor growth.
- In RCC,  $\alpha 5\beta 1$  is expressed on tumor cells and tumor stroma in addition to the vasculature. Furthermore, increased expression of  $\alpha 5\beta 1$  is seen on the tumor epithelium and stroma with worsening clinical grade.

## OBJECTIVES

- To evaluate the efficacy (tumor response) of volociximab as a single agent in patients with metastatic RCC, as defined by RECIST criteria.
- To evaluate time to disease progression and overall survival.
- To evaluate the PK and immunogenicity of volociximab.

## STUDY DESIGN

- This is a Phase II, open label, multicenter, two-cohort study designed to evaluate the efficacy and safety of volociximab in adult patients with metastatic RCC.
- Patients receive volociximab (10 mg/kg q2w in cohort 1 or 15 mg/kg qw in cohort 2) as an IV infusion for up to 2 years or until disease progression, whichever occurs first.
- The treatment period for this study is up to a total of 2 years. Patients will stay on treatment until they have progressive disease or unacceptable toxicity, or choose to withdraw, at which point they will exit the treatment phase.
- Every 8 weeks, a comprehensive disease assessment will be performed to evaluate tumor response using RECIST.
- These results are from the 10 mg/kg q2w cohort only.

## DEMOGRAPHICS

Patient characteristics	N (%)
Median age = 62.8 years	
<b>ECOG performance score</b>	
0	27 (67.5)
1	13 (32.5)
<b>Prior therapy</b>	
No prior therapy	2 (5)
1 prior therapy	18 (45)
$\geq 2$ prior therapies	20 (50)
<b>Prior radiation</b>	
Yes	10 (25)
No	30 (75)
<b>Prior immunotherapy</b>	
Yes	24 (60)
No	16 (40)
<b>Prior other therapy</b>	
Anti-angiogenic therapy	21 (52.5)
<b>Risk Factors</b>	
Prior nephrectomy	38 (95)
Corrected Calcium > 10 mg/dl	11 (27.5)
Hgb < 11.5 g/dL	8 (20)
LDH > 1.5 ULN	2 (5)
ECOG $\geq 2$	0 (0)

## RESULTS

❖ These results are from the 10 mg/kg q2w cohort only

Table 1

Best Overall Response	N = 40
	N (%)
CR	0 (0)
PR	1 (2.5)
SD	32 (80)
PD	7 (17.5)

Figure 1

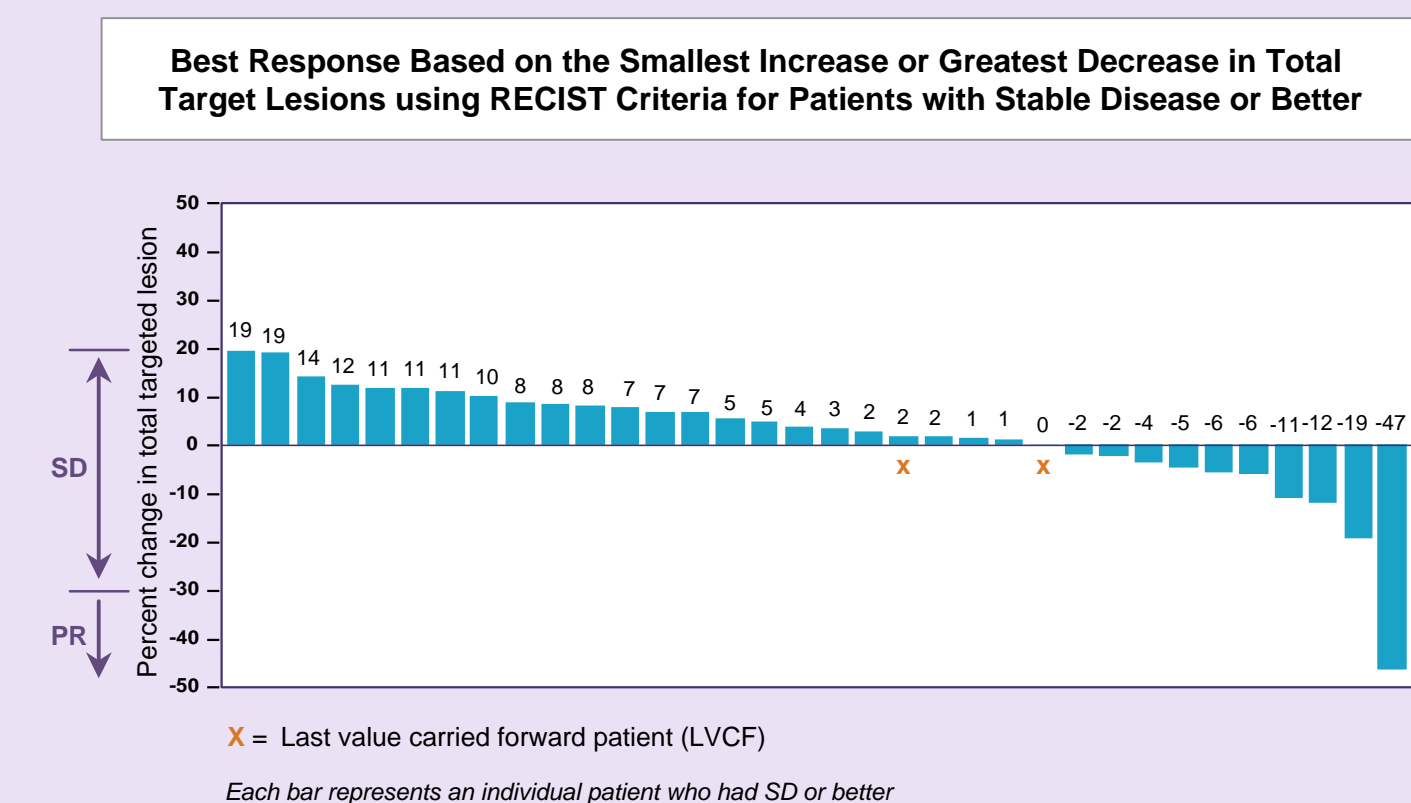


Figure 2

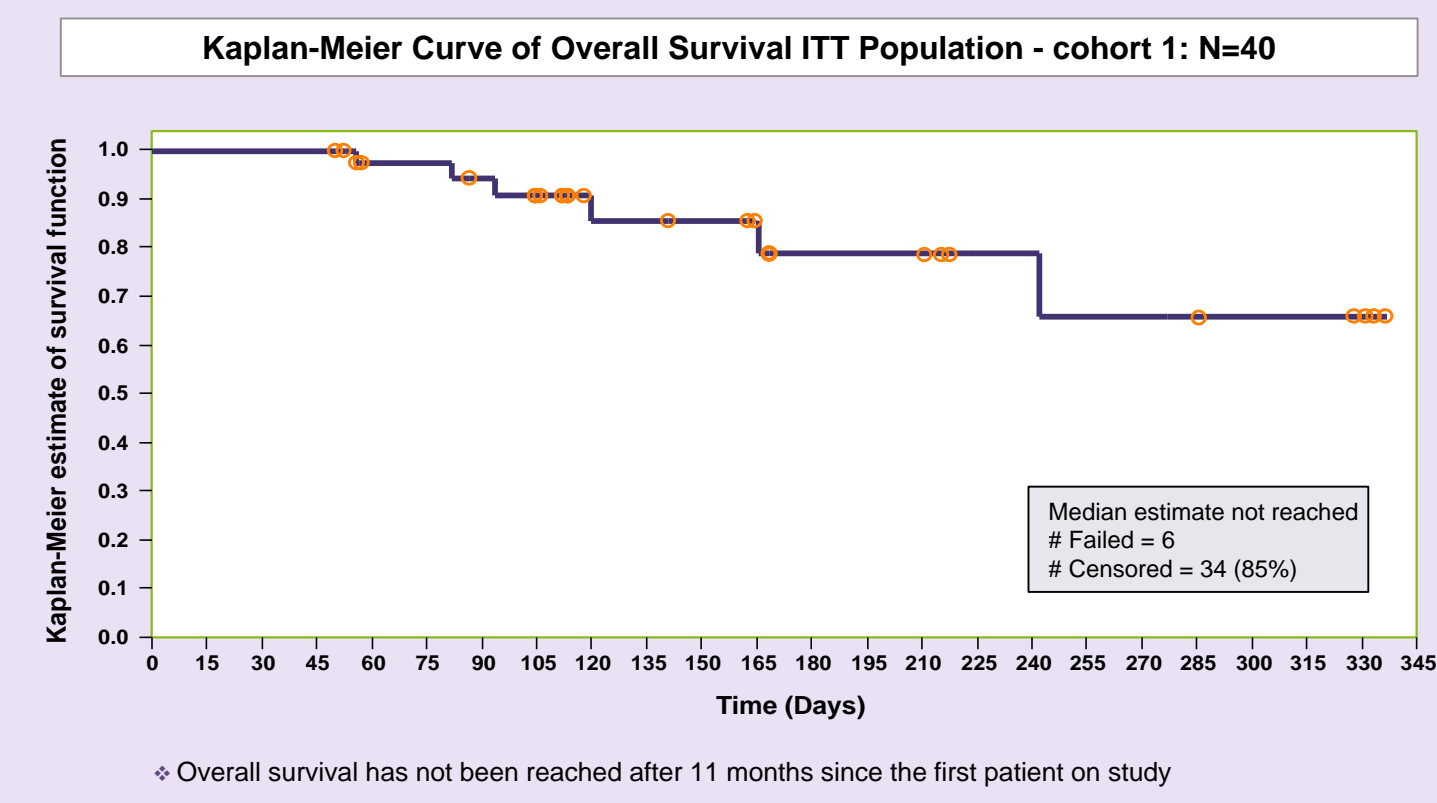


Figure 3

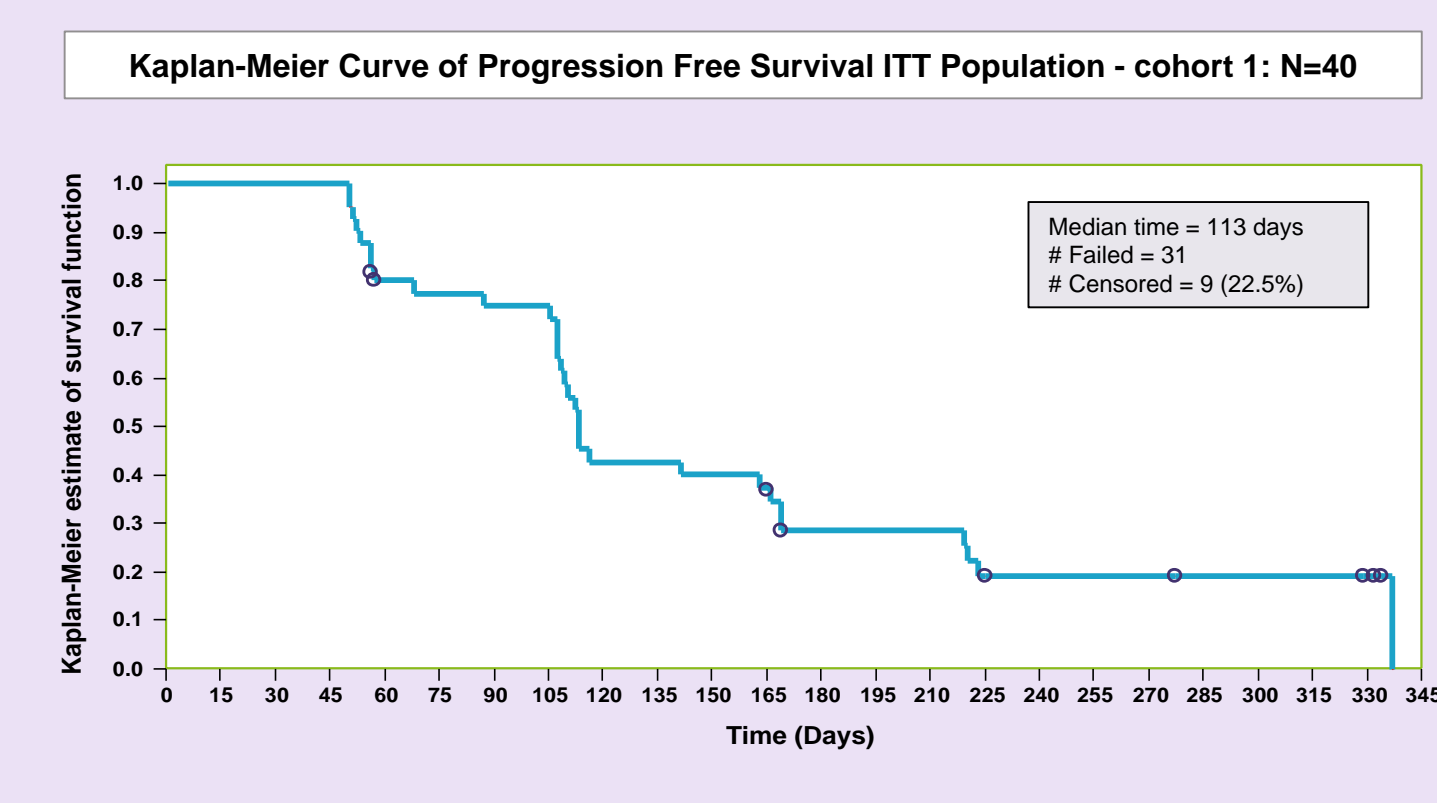
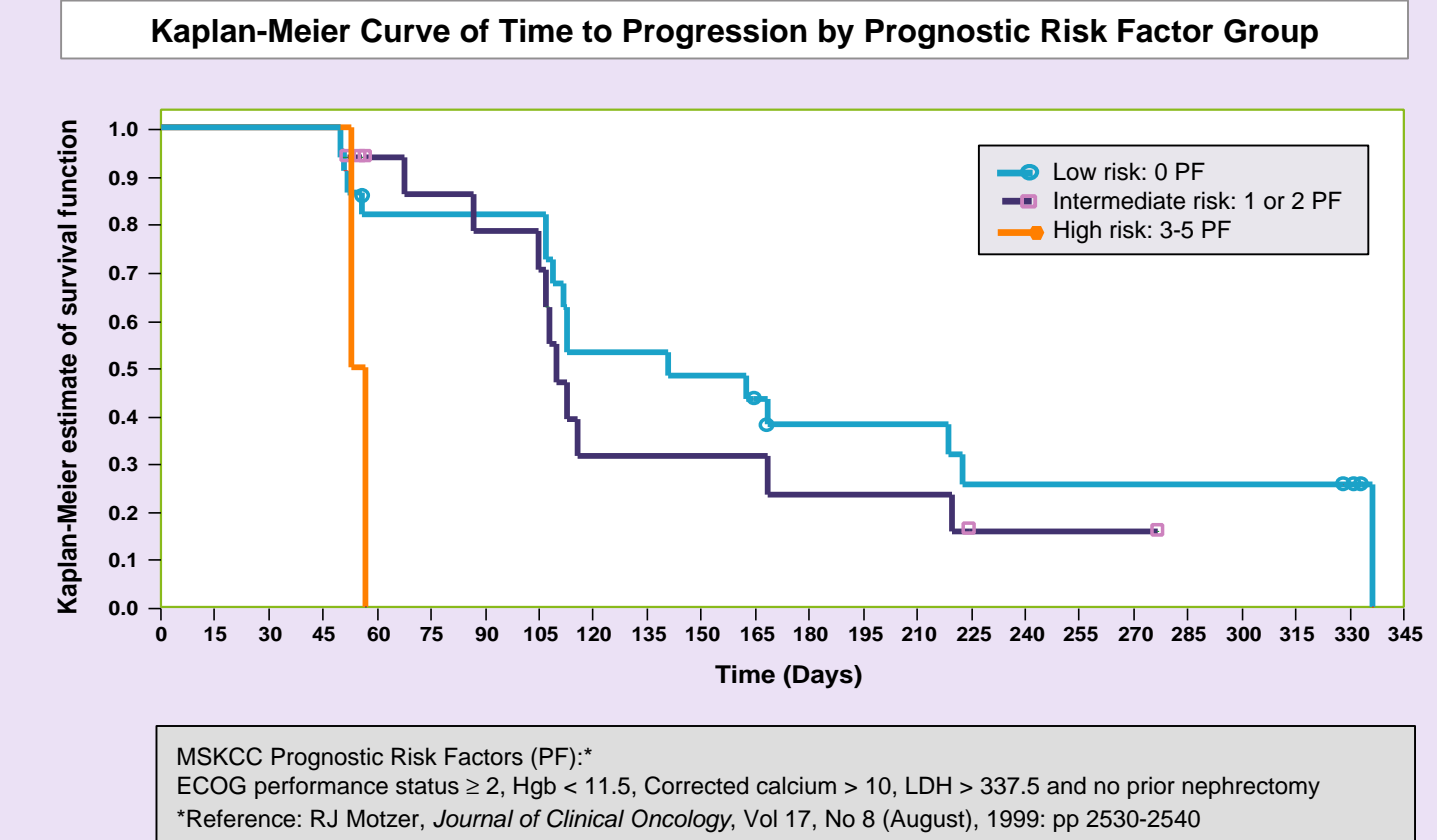


Figure 4



## RESULTS

Figure 5

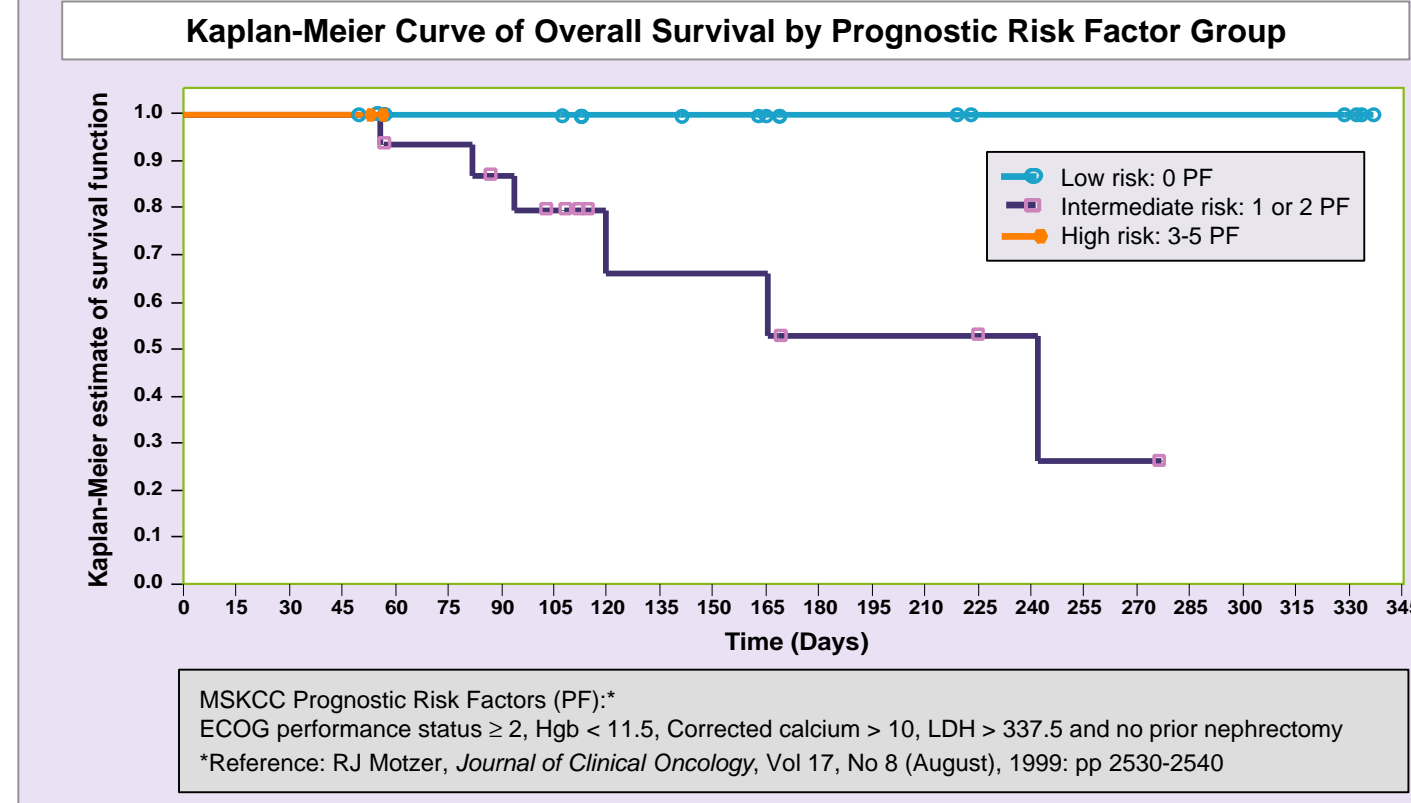


Table 2

	Survival Based on Prior Therapy		
	All pts N=40	Prior anti-angiogenic therapy N=21	Prior anti-angiogenic therapy excluded N=19
Median PFS	3.7 mo	3.7 mo	3.7 mo
Median OS	Not reached after 11 mo	8 mo	Not reached after 11 mo

Figure 6

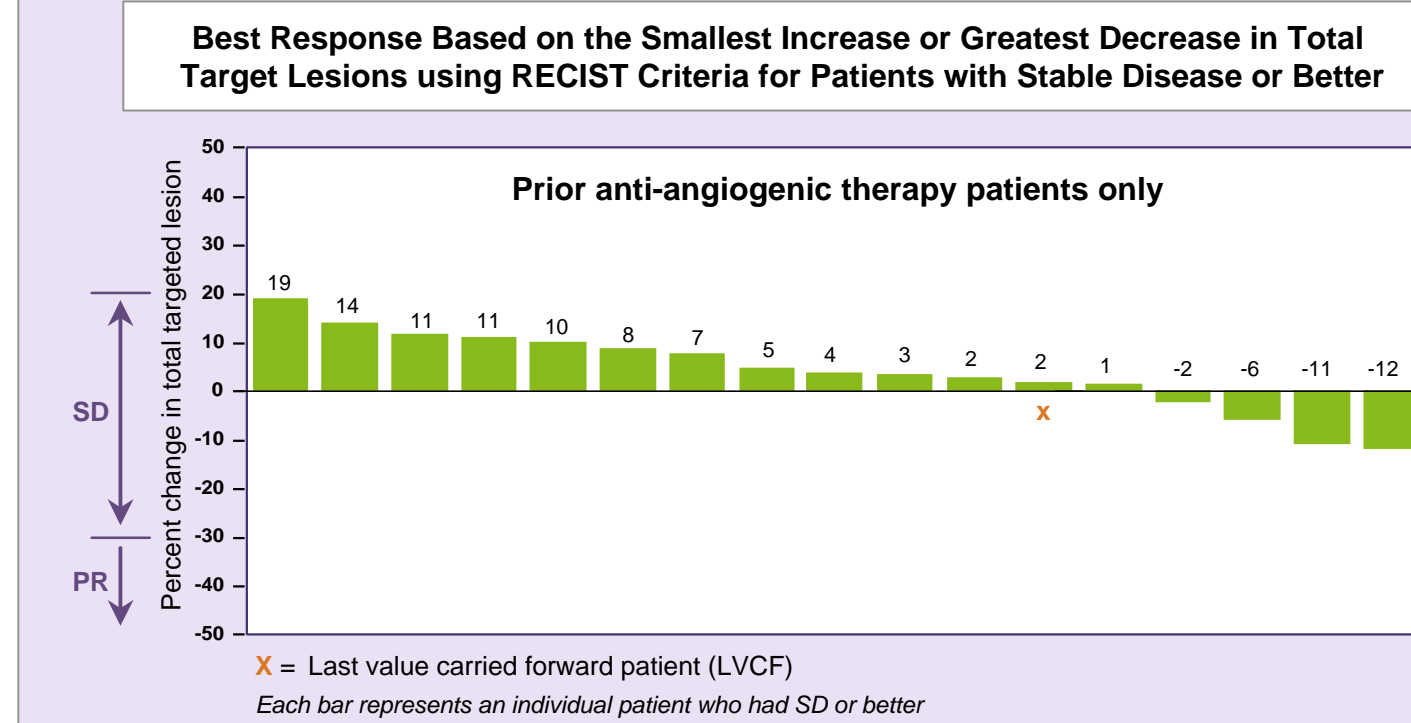


Figure 7

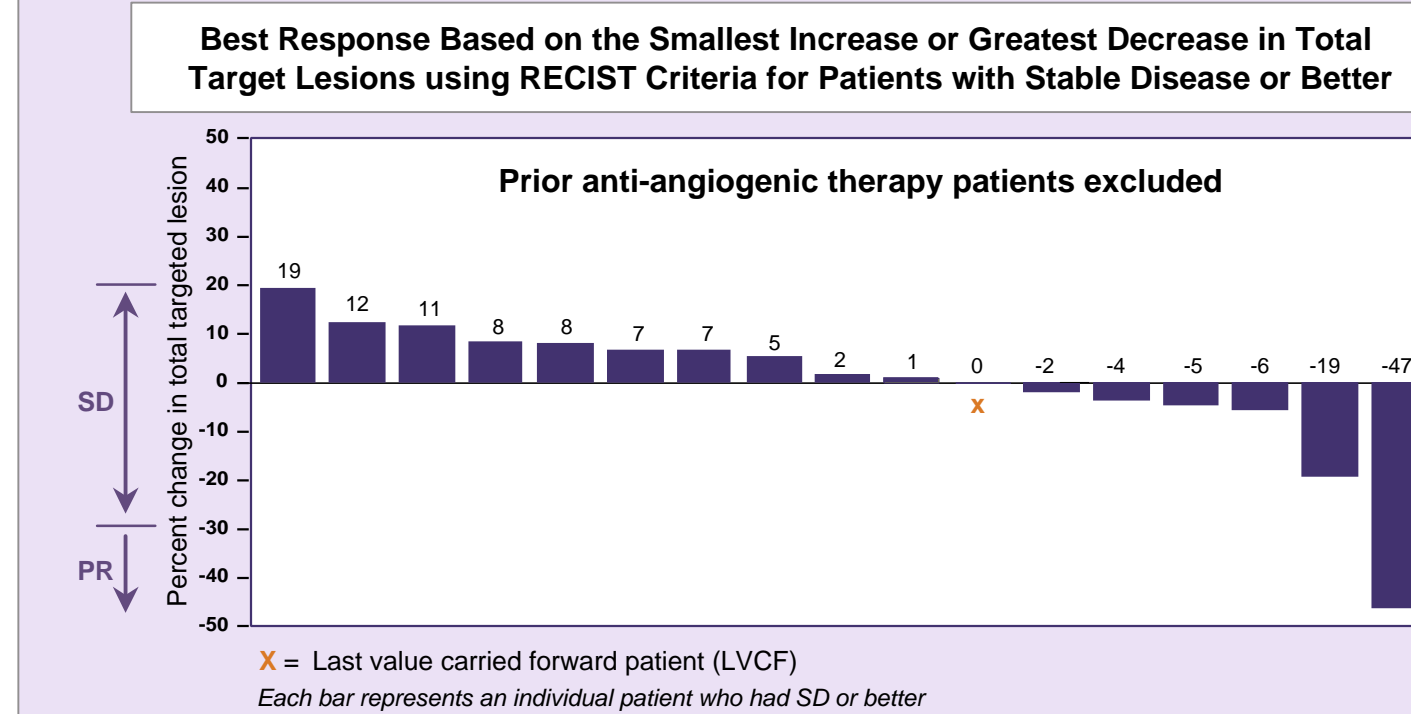


Table 3

**All Adverse Events in  $\geq 10\%$  of Subjects**

MedDRA Preferred Term	N = 40
Fatigue	25 (62.5%)
Nausea	13 (32.5%)
Dyspnea	7 (17.5%)
Pain in extremity	7 (17.5%)
Arthralgia	6 (15.0%)
Headache	6 (15.0%)
Abdominal pain	5 (12.5%)
Back pain	5 (12.5%)
Cough	5 (12.5%)
Diarrhea	5 (12.5%)
Edema peripheral	5 (12.5%)
Dyspepsia	4 (10.0%)
Hypertension	4 (10.0%)
Rash	4 (10.0%)
Vomiting	4 (10.0%)

## Summary of Grade 3/4 AEs/SAEs/Deaths

Number of subjects who reported at least one AE/SAE

- Grade 3 AEs:** 8 patients (20%), possibly related (3 pts): 1 hyperkalemia, dehydration & hyponatremia, 1 ascites, and 1 anemia.
- Grade 4 AE:** 1 patient (2.5%), not related.
- SAEs:** 6 patients (15%), possibly related (2 pts): 1 hyperkalemia and dehydration, and 1 hyponatremia.
- Deaths:** 6 patients (15%), 5 due to progressive disease, and 1 unrelated arrhythmia.

## CONCLUSIONS

- Volociximab is well tolerated at 10 mg/kg q2w as a single agent in refractory clear cell renal cell carcinoma.
- A higher dose of volociximab is currently being evaluated.
- Anti-tumor activity, defined as PR/SD at week 8, was observed in 83% of heavily pretreated patients and overall survival has yet to be reached after 11+ months.