

# Phase II Study of Volociximab (M200), an $\alpha 5\beta 1$ Anti-Integrin Antibody in Metastatic Melanoma

L. D. Cranmer<sup>1</sup>, A. Y. Bedikian<sup>2</sup>, A. Ribas<sup>3</sup>, S. O'Day<sup>4</sup>, A. Forero-Torres<sup>5</sup>, S. Yazji<sup>6</sup>, J. M. Kirkwood<sup>7</sup>; <sup>1</sup>University of Arizona/Arizona Cancer Center, Tucson, AZ; <sup>2</sup>MD Anderson Cancer Center, Houston, TX; <sup>3</sup>UCLA, Los Angeles, CA; <sup>4</sup>The Angeles Clinic and Research Foundation, Santa Monica, CA; <sup>5</sup>University of Alabama at Birmingham, Birmingham, AL; <sup>6</sup>PDL BioPharma, Fremont, CA; <sup>7</sup>Hillman Cancer Research Pavilion, Pittsburgh, PA

## ABSTRACT

**Background:** Integrin  $\alpha 5\beta 1$  has been reported to be upregulated in metastatic melanoma and in tumor angiogenesis. A critical survival step in angiogenesis is the ligation of fibronectin in the extracellular matrix to  $\alpha 5\beta 1$  on endothelial cells. M200 is an IgG4 chimeric monoclonal antibody targeting  $\alpha 5\beta 1$ , 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) in metastatic melanoma. Pts received M200 10 mg/kg IV every 2 weeks with DTIC 1g/m<sup>2</sup> monthly until disease progression. Pts were evaluated for efficacy every 8 weeks by objective response using RECIST criteria. Additional evaluations included pharmacokinetics and immunogenicity profile. An independent data safety monitoring board was utilized to review safety data.

**Results:** A total of 40 pts have been enrolled to date. All pts were evaluable for safety and 30 pts for objective response using ITT population. Median age was 58.8 years, with 26 (65%) male. ECOG score was 0-1 in 37 (92%) pts. Up to 14 doses of M200 (median 4 doses) and 7 doses of DTIC (median 2) have currently been administered, with dosing continuing. Thirty-one (77.5%) pts have had at least 1 AE with 8 (20%) pts at least 1 SAE. The most frequent adverse events for M200 were nausea 17.5%, constipation 10% and vomiting 10% and for DTIC were nausea 35%, vomiting 20% and pyrexia 15%. Fifteen SAE's with 2 possibly related to M200 including hypertension and deep vein thrombosis. Four pts died in the study, all with progressive disease (PD). Best overall response at 8 weeks was stable disease (SD) in 16/30 pts and PD in 14/30 pts. Median time to progression was 72 days.

**Conclusion:** M200 appears to be well tolerated at 10 mg/kg q2w in combination with DTIC.

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.
- The mechanism of action of volociximab is distinct from that of other anti-angiogenic agents because it acts downstream and is independent of the growth factors that stimulate angiogenesis, such as vascular endothelial growth factor (VEGF) and bFGF.
- Volociximab binds to  $\alpha 5\beta 1$  integrin and blocks the ligation of its ligand fibronectin and induces apoptosis of proliferating endothelial cells.
- In melanoma,  $\alpha 5\beta 1$  is expressed on tumor cells and stroma as well as on the vasculature. Furthermore, it appears that  $\alpha 5\beta 1$  is upregulated on the tumor cells as they become invasive.

## OBJECTIVES

- To evaluate the efficacy (tumor response) of volociximab in combination with DTIC in patients with metastatic melanoma using RECIST criteria.
- To evaluate time of disease progression and overall survival.
- To evaluate the PK and immunogenicity of volociximab.

## STUDY DESIGN

- This is a Phase II, open label, multicenter, single-arm study to evaluate the efficacy and safety of volociximab in combination with DTIC in adult patients with metastatic melanoma.
- Patients received volociximab (10 mg/kg) as an IV infusion every other week for up to 104 weeks or until disease progression, whichever occurred first.
- Patients also received standard chemotherapy with DTIC for up to 27 cycles or until disease progression, whichever occurred first. Each cycle consisted of one dose of DTIC (1 g/m<sup>2</sup>) administered intravenously over one hour once every 4 weeks.
- Every 8 weeks a comprehensive disease assessment was performed to evaluate tumor response using RECIST.

## DEMOGRAPHICS

Patient characteristics	N (%)
Median age = 58.8 years	
Male	26 (65)
Female	14 (35)
<b>ECOG performance score</b>	
0	30 (75)
1	10 (25)
<b>Prior melanoma therapy</b>	
surgery	37 (92.5)
bioimmunotherapy	18 (45)
interferon-alpha	13 (32.5)
radiation therapy	10 (25)
other	6 (15)
<b>Tumor classification</b>	
M1a	3 (7.5)
M1b	10 (25)
M1c	22 (55)
unknown	5 (12.5)
<b>Time since first diagnosis</b>	
Median = 3.5 years	

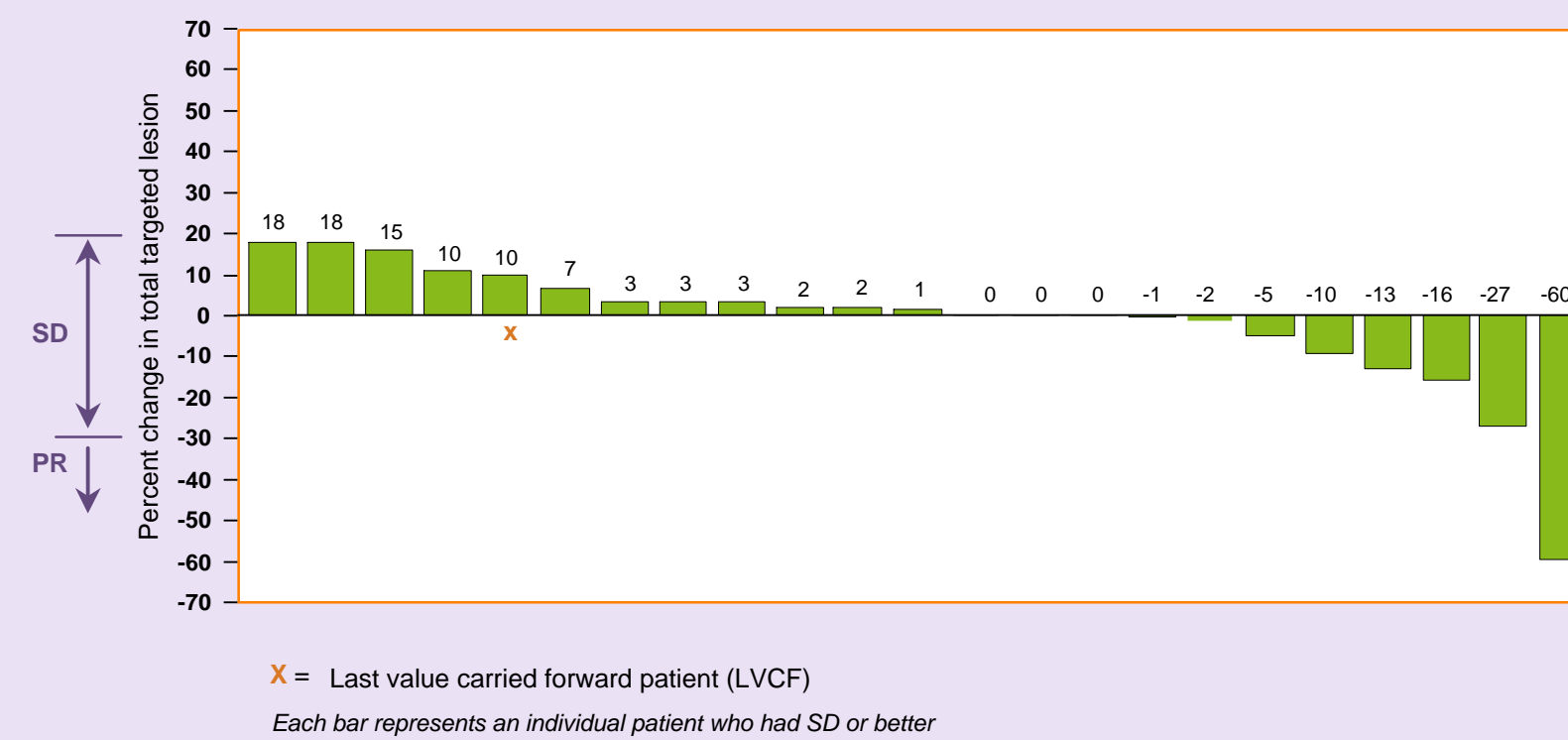
## RESULTS

Table 1

Best Overall Response	N = 37
	N (%)
CR	0 (0)
PR	1 (2.7)
SD	22 (59.5)
PD	14 (37.8)

Figure 1

Best Response Based on the Smallest Increase or Greatest Decrease in Total Target Lesions using RECIST Criteria for Patients with Stable Disease or Better



## RESULTS

Figure 2

Kaplan-Meier Curve of Progression Free Survival ITT Population - cohort 1: N=37

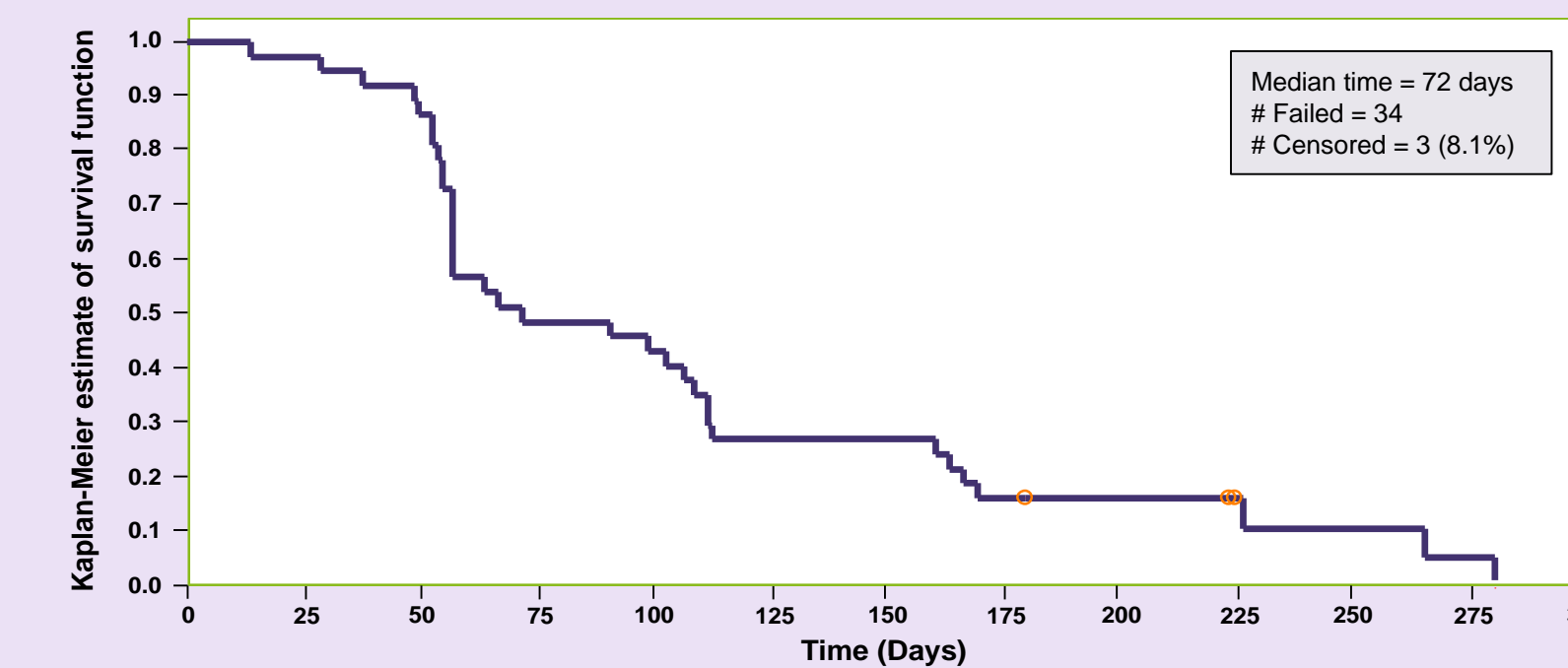


Figure 3

Kaplan-Meier Curve of Overall Survival ITT Population - cohort 1: N=40

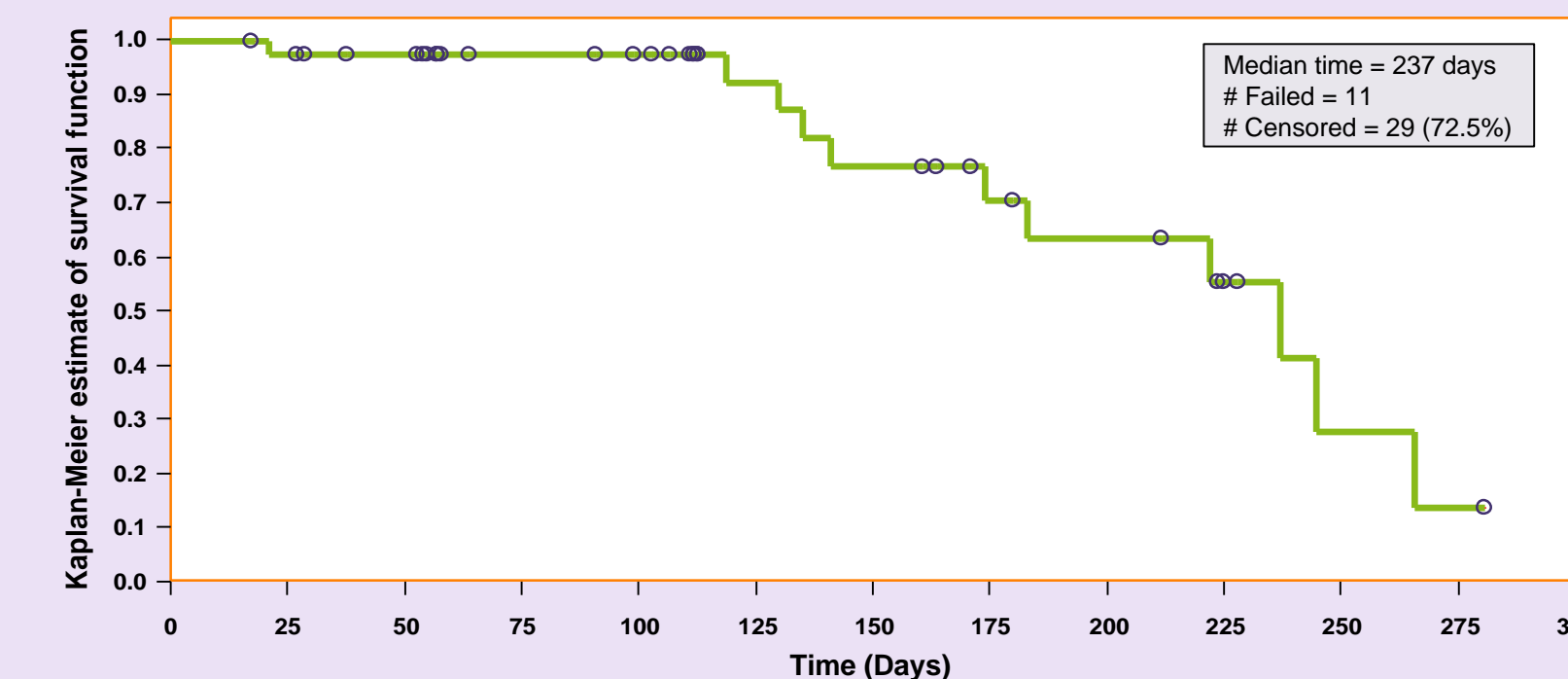


Table 2

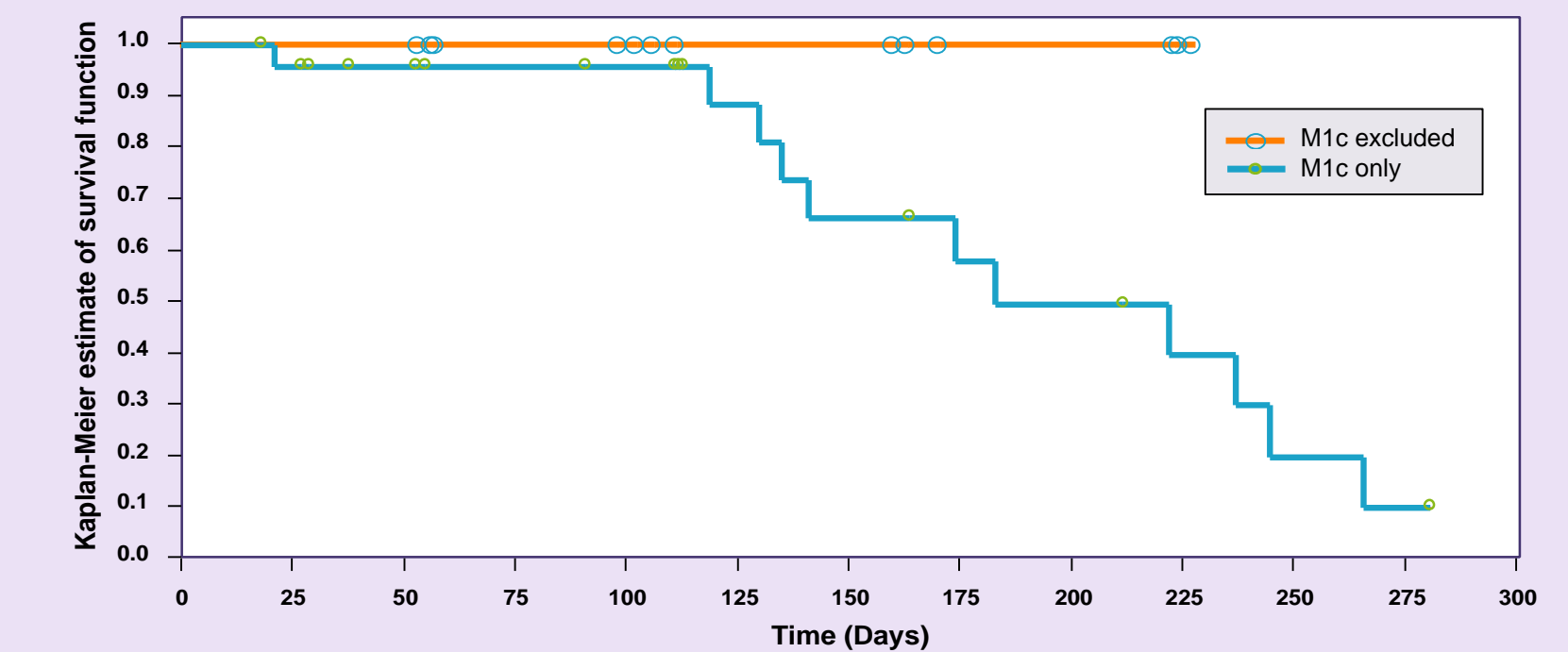
N (%)	Survival Based on Tumor Classification		
	All pts 37 (92)	M1a* and M1b 13 (32)	M1c pts only 22 (55)
Median PFS	2.4 mo	3.7 mo	1.9 mo
Median OS	7.9 mo	Not reached after 7.5 mo	6.1 mo

M1a distant skin, subcutaneous, or nodal mets  
M1b lung metastases  
M1c All other visceral metastases or any distant metastases with elevated LDH  
Reference: CM Balch, *Journal of Clinical Oncology*, Vol 19, No 16 (August 15), 2001: pp 3635-3648

\*only 3 patients classified as M1a

Figure 4

Kaplan-Meier Curve of Overall Survival



M1c patients excluded median OS has not been reached after 7.5 months  
M1c patients only median OS 6.1 months  
Reference: CM Balch, *Journal of Clinical Oncology*, Vol 19, No 16 (August 15), 2001: pp 3635-3648

Table 3

All Adverse Events in <sup>≥</sup> 10% of Subjects	
MedDRA Preferred Term	N = 40
Nausea	20 (50.0%)
Fatigue	17 (42.5%)
Injection site irritation	12 (30.0%)
Vomiting	12 (30.0%)
Constipation	11 (27.5%)
Arthralgia	8 (20.0%)
Diarrhea	8 (20.0%)
Pain in extremity	7 (17.5%)
Pyrexia	7 (17.5%)
Anorexia	6 (15.0%)
Edema peripheral	6 (15.0%)
Chills	5 (12.5%)
Dyspnea	5 (12.5%)
Back pain	4 (10.0%)
Pain	4 (10.0%)

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

Number of subjects who reported at least one AE/SAE

- Grade 3 AEs:** 10 patients (25%), possibly related (2 pts): 1 portal vein occlusion and 1 dyspnea.
- Grade 4 AE:** 1 patient (2.5%), not related.
- SAEs:** 10 patients (25%), possibly related (2 pts): 1 deep vein thrombosis and 1 dyspnea.
- Deaths:** 11 patients (55%), all due to progressive disease.

## CONCLUSIONS

- Volociximab is well tolerated at 10 mg/kg q2w in combination with DTIC.
- Higher doses of volociximab are currently being evaluated.
- Anti-tumor activity, defined as PR/SD at week 8, was observed in 62%, and median overall survival of 7.9 months in a population of which 55% had poor prognosis stage M1c classification.
- Additional evaluation of volociximab in melanoma is planned.