

Phase II Study of Volociximab (M200), an $\alpha 5\beta 1$ Anti-integrin Antibody in Metastatic Adenocarcinoma of the Pancreas (MPC)

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ABSTRACT

Background: Tumor angiogenesis occurs when pro-angiogenic growth factors are released, stimulating endothelial cell proliferation and migration to form neovessels. A critical survival step for 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 $\alpha 5\beta 1$, 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) in MPC. Pts received M200 10 mg/kg IV every 2 weeks with Gemcitabine (Gem) 3 weeks on 1 week off for up to 13 cycles or 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 20 pts have been enrolled. All pts were evaluable for safety and 16 pts for objective response (to date) using ITT population. Median age was 59.8 years. ECOG score was 0-1 in 19 (95%) and 2 in 1 (5%) pts. The most frequent side effects for M200 were vomiting in 7 (35%) pts and nausea in 8 (40%) pts and for (Gem) were nausea in 8 (40%) pts and vomiting in 8 (40%) pts. Eight pts died in the study, seven with progressive disease and 1 with GI perforation (possibly related to M200). One partial response was noted to date. Best overall response was (PR) 1/16 and stable disease in 8/16 pts. Median time to progression was 112+ days.

Conclusions: M200 appears to be well tolerated at 10 mg/kg q2w in combination with (Gem). Based on preliminary data from this trial and safety data from other trials, a higher dose level of M200 will be explored.

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 inhibition for the treatment of solid tumors.
- Volociximab binds to $\alpha 5\beta 1$ integrin and inhibits the ligation of $\alpha 5\beta 1$ to fibronectin, thereby inhibiting a pivotal interaction required for angiogenesis. The mechanism of action is distinct because it acts downstream of the growth factors that stimulate angiogenesis, such as VEGF and bFGF.
- Volociximab differs from other angiogenesis inhibitors currently approved or in clinical trials, which primarily focus on inhibiting the vascular endothelial growth factor (VEGF) pathway.
- $\alpha 5\beta 1$ expression is seen in pancreatic cancer on vasculature as well as tumor epithelium.

OBJECTIVES

- Primary**
- To evaluate the efficacy (tumor response) of volociximab in combination with gemcitabine in patients with metastatic pancreatic cancer by RECIST criteria.
- Secondary**
- 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, multi-center, 2-sequential-cohort study to evaluate the efficacy and safety of volociximab in combination with gemcitabine in chemotherapy naïve adult patients with metastatic pancreatic adenocarcinoma.
- 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. Patients also receive standard chemotherapy with gemcitabine for up to 26 cycles 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.

DEMOGRAPHICS

Patient characteristics	N (%)
Median age =	59.8 years
Male	11 (55)
Female	9 (45)
ECOG performance score	
0	5 (25)
1	14 (70)
2	1 (5)
Disease classification	
stage IV metastatic	20 (100)
locally advanced	0 (0)

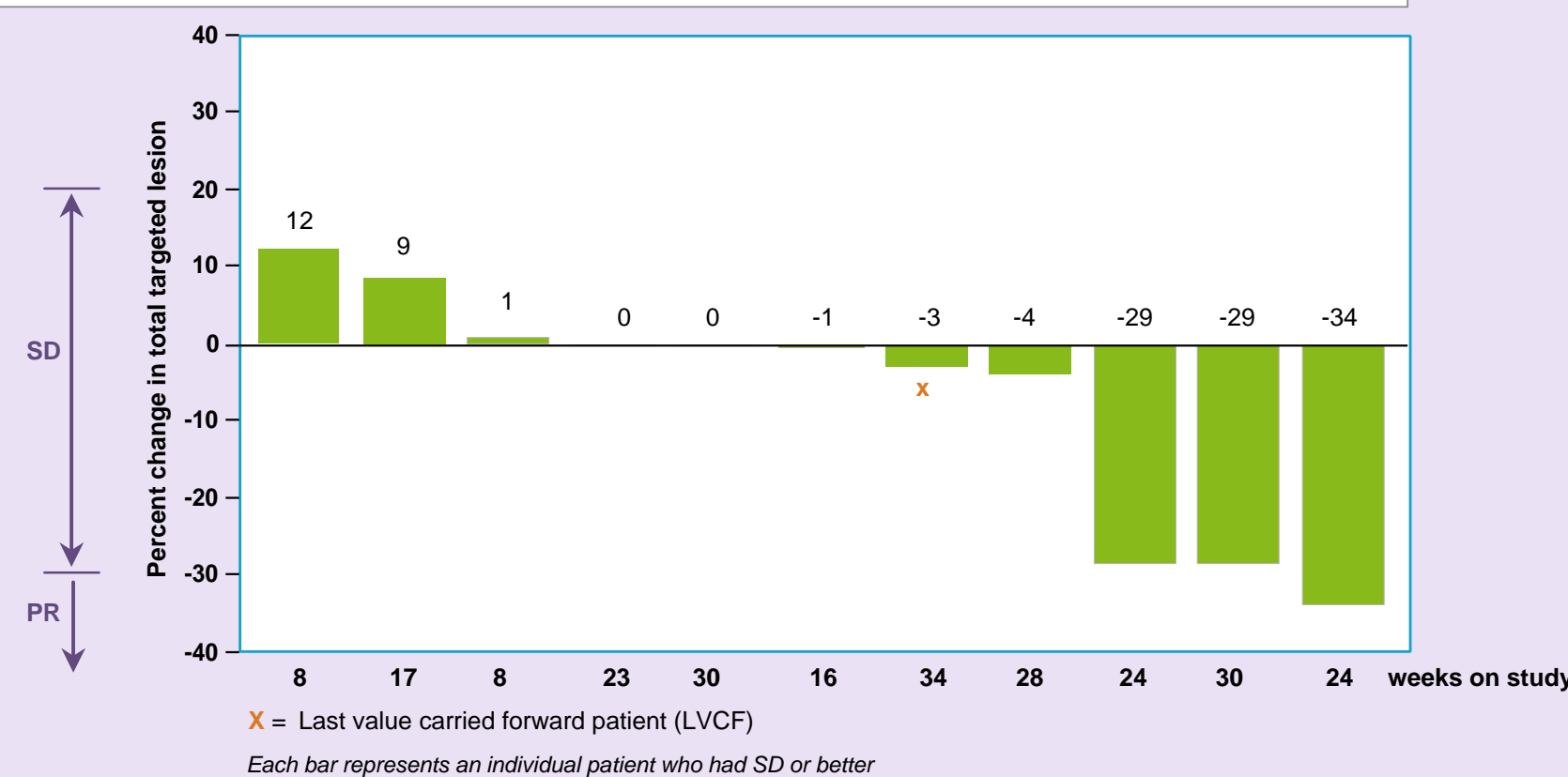
RESULTS

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

Best Overall Response	N = 19*
	N (%)
CR	0 (0)
PR	1 (5.3)
SD	10 (52.6)
PD	8 (42.1)

* 1 patient died before the first assessment

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 Time to Progression ITT Population – cohort 1: N=20

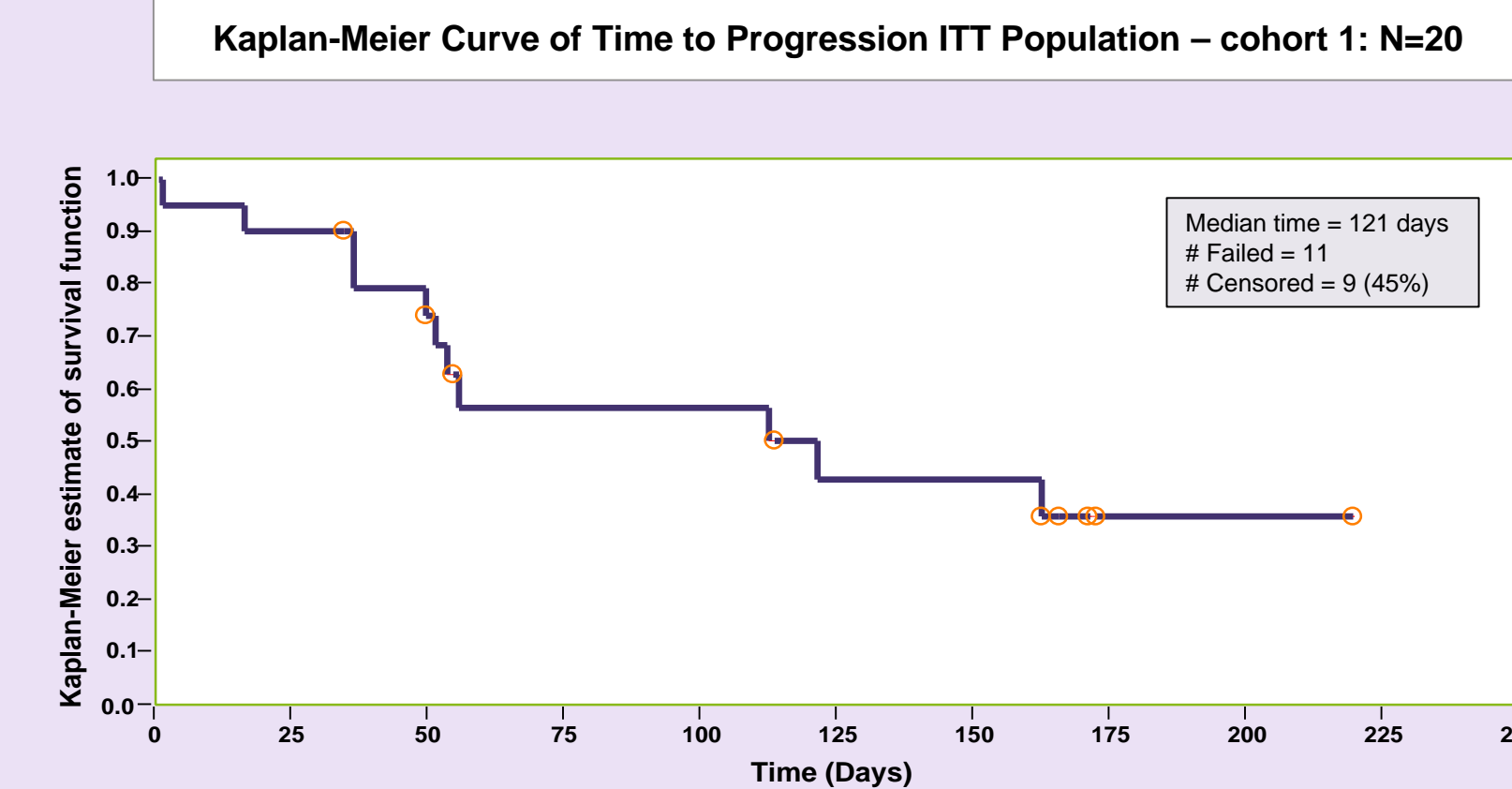


Figure 3
Kaplan-Meier Curve of Overall Survival ITT Population – cohort 1: N=20

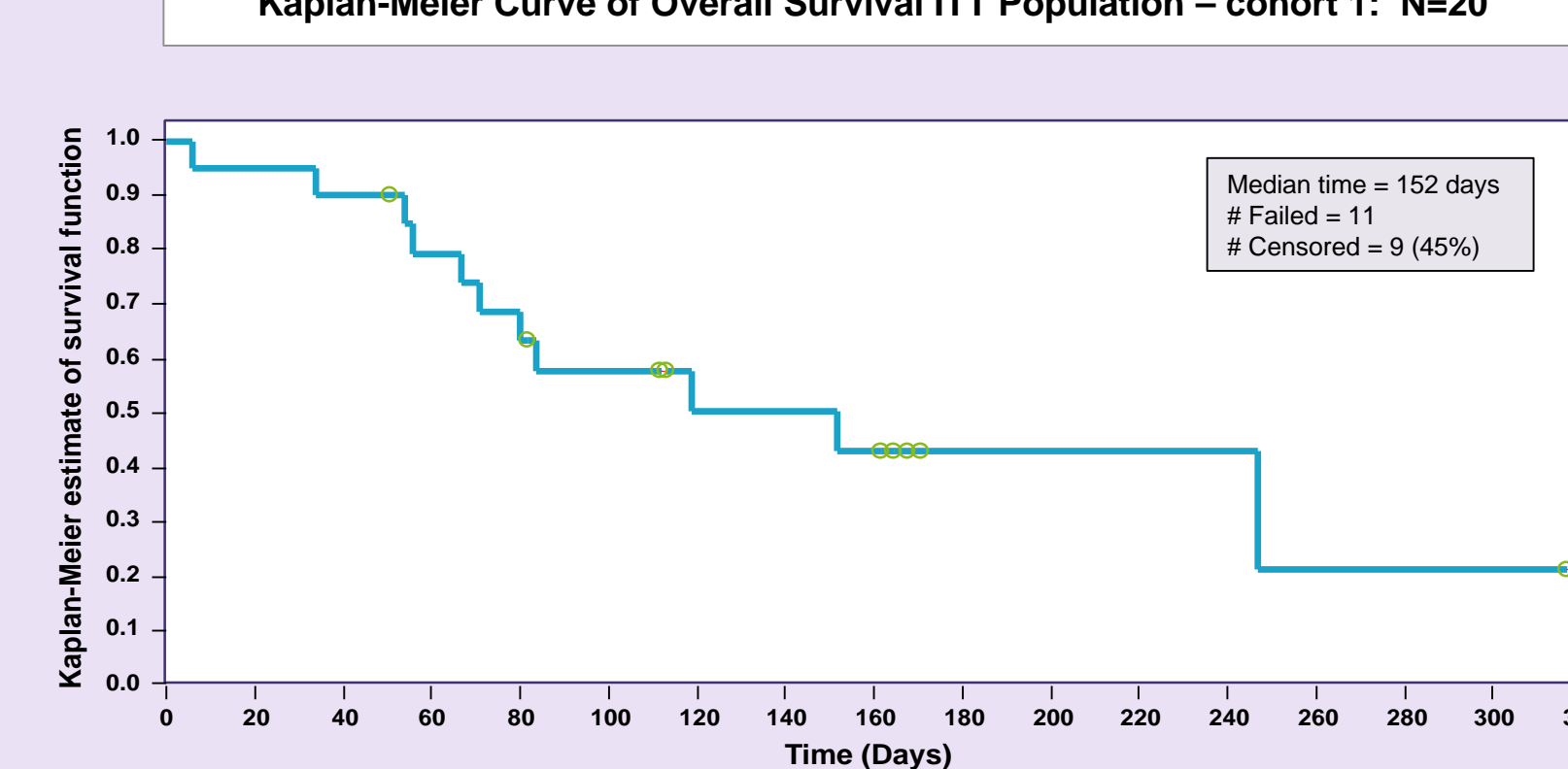


Table 2
Survival Based on Eligible Patients

N (%)	All pts N=20	Eligible patients* N=14
Median TTP	4 mo	5.4 mo
Median OS	5 mo	8.2 mo

*Refers to patients who fulfilled all eligibility criteria (6 patients were treated on study, but were granted waivers on entry criteria due to on more of the following: PS ≥ 2 , low Hgb, high LDH or abnormal PT/PTT)

Table 3
All Adverse Events in $\geq 10\%$ of Subjects

MedDRA Preferred Term	N = 20
Nausea	13 (65.0%)
Vomiting	12 (60.0%)
Constipation	10 (50.0%)
Lethargy	9 (45.0%)
Diarrhea	8 (40.0%)
Edema peripheral	7 (35.0%)
Influenza like illness	6 (30.0%)
Pyrexia	6 (30.0%)
Abdominal pain upper	5 (25.0%)
Anorexia	5 (25.0%)
Fatigue	5 (25.0%)
Abdominal pain	4 (20.0%)
Dyspepsia	4 (20.0%)
Headache	4 (20.0%)
Anemia	3 (15.0%)
Chills	3 (15.0%)
Dehydration	3 (15.0%)
Dyspnea	3 (15.0%)
Myalgia	3 (15.0%)
Neutropenia	3 (15.0%)
Rash	3 (15.0%)
Weight decreased	3 (15.0%)
Ascites	2 (10.0%)
Blood bilirubin increased	2 (10.0%)
Decreased appetite	2 (10.0%)
Insomnia	2 (10.0%)

Table 4
Summary of Grades 3 and 4 Adverse Events Possibly, Probably or Related to Volociximab

MedDRA Preferred Term	Grade 3	Grade 4
Lethargy	1 (5.0%)	0
Diarrhea	1 (5.0%)	0
Neutropenia	1 (5.0%)	1 (5.0%)
Vomiting	1 (5.0%)	0
Asthenia	1 (5.0%)	0
Fatigue	1 (5.0%)	0
Gastrointestinal perforation	0	1 (5.0%)
Pulmonary embolism	0	1 (5.0%)

Summary of Grade 3/4 AEs/SAEs/Deaths

Number of subjects who reported at least one AE/SAE

- Grade 3 AEs:** 10 patients (50%), possibly or probably related (6 pts): 2 neutropenia, 1 diarrhea, 1 vomiting, 1 fatigue and asthenia, and 1 lethargy.
- Grade 4 AEs:** 6 patients (30%), possibly or probably related (3 pts): 1 neutropenia, 1 GI perforation, and 1 pulmonary embolism.
- SAEs:** 12 patients (60%), possibly or probably related (7 pts): 3 diarrhea, nausea and vomiting, 1 GI perforation, 1 asthenia, 1 lethargy, and 1 pulmonary embolism.
- Deaths:** 10 patients (50%), 8 progressive disease, 1 pulmonary embolism, and 1 GI perforation.

CONCLUSIONS

- Volociximab is well tolerated at 10 mg/kg q2w when added to a conventional schedule of gemcitabine.
- For patients who met the entry criteria, median overall survival of 8.2 months and time to progression of 5.4 months has been observed.
- Additional patients are being enrolled in the study at 15 mg/kg qw.
- Anti-tumor activity, defined as PR/SD at week 8, was observed in 58% of patients.

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