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A phase II study of sorafenib in malignant mesothelioma: results of CALGB 30307

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Abstract

Hypothesis—Malignant mesotheliomas (MM) express VEGFR, PDGFR, and cKIT. Sorafenib is a potent inhibitor of the RAS/RAF/MEK pathway and also targets VEGFR and cKIT. We evaluated the activity of sorafenib in patients with unresectable mesothelioma.

Methods—MM patients who had received 0 to 1 prior chemotherapy regimens were treated with sorafenib 400mg orally twice daily continuously. The primary endpoint was objective response. ERK1/2 phosphorylation in archival tissues was correlated with response and survival.

Results—51 patients were enrolled, 50 were evaluable and included in analysis. Three patients had a partial response (6% (95% CI 1.3–16.6%)), and 27 (54%(95% CI 39.3–68.2%)) had stable disease. Median progression-free survival and median overall survival were 3.6 months and 9.7 months, respectively. Median survival was superior in epithelioid histology versus other types (10.7 months versus 3.7 months, p=0.0179). The difference in median overall survival between pre-treated and chemo-naive patients was not statistically significant (13.2 months versus 5 months, p=0.3117). Low/negative baseline tumor phospho-ERK1/2 levels were associated with improved overall survival (13.9 months versus 5.2 months; p=0.0066).

Conclusion—Sorafenib has limited activity in advanced MM patients, similar to that seen in with other VEFGR tyrosine kinase inhibitors. Additional studies of sorafenib in MM are not warranted.

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Keywords

mesothelioma; sorafenib; vascular endothelial growth factor; tyrosine kinase inhibitor; clinical trial

INTRODUCTION

The median survival of patients with unresectable malignant mesothelioma is a year or less[1]. The only FDA approved treatment in this disease is the combination of cisplatin with pemetrexed, which achieves a response rate (RR) of 41%, time to progression (TTP) of 6 months, and median overall survival (OS) of 12 months[1]. There are no approved agents for patients who progress after first-line chemotherapy.

Vascular endothelial growth factor (VEGF), is a mitogen for vascular endothelial cells. Acting through its receptors VEGFR-1(Flt-1) and VEGFR-2 (KDR), VEGF is necessary for maintenance of tumor vasculature[2]. Treatment of mesothelioma cell lines with recombinant human VEGF results in phosphorylation of VEGFR-1 and KDR and induces proliferation of mesothelial cells[3], while the addition of VEGF neutralizing antibodies inhibits this proliferative effect. Serum VEGF levels and tumor microvessel density correlate in patients with mesothelioma inversely with survival[3, 4]. VEGF also acts through Raf/Mek/Erk kinase pathways[5]. Multiple growth factor receptors that act through the Ras/Raf/Mek/Erk pathway such as EGFR, IGF-1R, PDGF BB and the receptor PDGFR β and VEGFR1/2 are over-expressed or aberrant in mesothelioma[3, 6–8].

Sorafenib (BAY 43–9006) is a potent inhibitor of the RAF/MEK/ERK signaling pathway with additional activity against VEGFR 2, PDGFR β, and cKIT[9]. It is an approved agent in the treatment of renal cell carcinoma[10] and hepatocellular carcinoma[11]. Given the selective inhibitory activity of sorafenib against Raf, VEGFR2, and PDGFR β, which are potential therapeutic targets in mesothelioma, a phase II study of sorafenib in unresectable mesothelioma was undertaken by the Cancer and Leukemia Group B (CALGB).

MATERIALS AND METHODS

Eligibility Criteria

Eligible patients had histologically confirmed malignant mesothelioma not amenable to curative surgery, including sarcomatoid, epitheloid, and mixed histologies of the pleura, peritoneum, pericardium and tunica vaginalis. Patients may have received no more than one pemetrexed-containing chemotherapy regimen. No prior tyrosine kinase/signal transduction/ angiogenesis inhibitor therapy was allowed. Any prior chemotherapy or radiation must have been administered ≥4 weeks earlier. Other eligibility criteria included: ECOG PS 0 or 1, measurable disease, no therapeutic anticoagulation, no currently active second malignancy (completed treatment with <30% risk of relapse) other than non-melanoma skin cancers and carcinoma in situ of the cervix, and lab values reflective of adequate organ function (granulocytes ≥1500/mm3, platelets ≥100,000/mm3, total bilirubin ≤1.5 X upper limit of normal (ULN), AST ≤2.5 xULN, creatinine≤1.5 X ULN, INR <1.5). Availability of pathology blocks or slides from a core surgical biopsy was required for evaluation of biological correlates. The study was approved by the Institutional Review Board at each center and all patients were required to sign informed consent.

Study treatment and evaluation

Sorafenib was administered orally at a fixed dose of 400 mg twice daily. Twenty-eight days of treatment constituted once cycle. Treatment was continued until disease progression or unacceptable toxicity. Dose modifications included dose level-1 (200mg twice daily) and -2 (200mg once daily). Dose modification was recommended for grade ≥3 toxicities that were attributable to sorafenib. No dose re-escalation was allowed. Evaluations included weekly blood pressure measurements during the first treatment cycle and CT scans after every two cycles of treatment. Disease burden was measured by RECIST criteria, and in patients with solely a pleural rind, the modified RECIST criteria were used[12].

Immunohistochemical analysis of tumor phospho-ERK 1/2 (p-ERK1/2) was performed on archival tissue with primary antibody p-ERK 1/2 (Thr202/Tyr204-Cell Signaling Technology). Staining of p-ERK 1/2 was based on intensity and degree of tumor staining. The results were subsequently divided into two categories: high/medium (group 1) and low/negative (group 2). *BRAF* mutation status was determined by amplification of exons 11 and 15 with flanking intronic primers followed by direct sequencing. Specific primer sequences are available upon request.

Statistical Methods

The primary endpoint of the study was objective response rate. Secondary endpoints included i) overall survival and progression free survival, ii) toxicities, and iii) correlation of BRAF mutations and p-ERK1/2 expression with anti-tumor activity. A one stage phase II design was used. A forty-four patient sample size was designed to differentiate response rates of 5% and 20% with 95% power by a two-sided test at 0.10 level of significance. It was assumed that two-thirds (n=29) of the patients would be treated on the study as second line therapy and would provide sufficient power for a subgroup analysis of outcome by line of treatment. Specifically 29 patients would provide an 86% power to differentiate between 5% and 20% response rate by a two-sided test at 0.10 level of significance. Response rate (complete/partial response) was calculated as well as its 95% confidence interval. Overall survival and progression free survival curve were estimated by Kaplan-Meier product limit method. The difference in OS and PFS between pre-treated vs. chemo naive patients was compared by log rank test, so as that between histological type (epitheloid vs. others). A step-wise multivariate cox regression with stay level of 0.15 and entry level of 0.20 was also performed adjusting for baseline covariates such as histological type (epitheloid vs. others), gender (female vs. male), performance status and age. For exploratory analysis of biological markers, Fisher's exact tests were performed to evaluate association between p-ERK1/2 expression and response. Cox models were fit to test the correlations between progression-free survival / overall survival and biomarker p-ERK 1/2 while adjusting for other baseline covariates such as histological type (epitheloid vs. others), gender (female vs. male), and age (continuous variable). A step-wise method was used with the same entry and stay criteria. Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. Statistical analyses were performed by CALGB statisticians.

RESULTS

Patient Characteristics

Fifty-one patients were enrolled between October 2004 and August 2005. One patient did not receive any treatment due to hospitalization for pain. All other patients are eligible and included in the analysis. Baseline characteristics of the patients are described in table 1. As expected for this disease, most patients were male. The most frequent histology was

epithelioid, and the pleura was the predominant site of involvement. Sixty percent (60%) of the patients had been previously-treated with pemetrexed-based chemotherapy.

A total of 252 cycles of sorafenib were administered to the 50 patients. The median number of treatment cycles administered was 3 (range 1–32). Patients who received prior chemotherapy underwent a median of 3.5 cycles (range 1–32) of chemotherapy while chemo-naïve patients received a median of 2 cycles (range 1–31) of chemotherapy (p=0.66)

Toxicity

Grade 3 and 4 toxicities are displayed in table 2. The most common grade 3 toxicity was fatigue followed by hand-foot syndrome. Grade 3 hypertension was uncommon occurring only in <5% of patients, and there were no incidences of grade 4 hypertension. The only grade 4 event was fatigue in one patient. There were no grade 5 toxicities. Five patients (10%) discontinued treatment due to toxicities. Sixteen patients (32 %) had dose reduction due to toxicity. Skin toxicity in ten patients and fatigue in eight patients were the most common reasons for dose reductions.

Efficacy outcomes

Response data are available for 50 patients. Three patients (6%, 95% CI 1.3–16.6%) had partial responses which lasted three, six, and six months. Stable disease occurred in 27 (54%, 95% CI 39.3, 68.2%) of patients. We failed to reject the null hypothesis that the response rate is 5% or less. The responses are illustrated as a waterfall plot in Figure 1, which shows that tumor shrinkage and growth was about equally distributed. The median duration of stable disease was 7.95 months (95% CI 3.58, 18.63). For patients with prior chemo, the response rate is (3.33%, 95% CI 0, 9.76%). For patients who are chemo naive, the response rate is (10%, 95% CI 0, 23%). At the time of this analysis three of the treated patients are still alive for whom the follow up times are 32, 37, and 40 months. Two of the three patients who demonstrated a response had not received prior chemotherapy.

The median progression-free survival (PFS) and overall survival (OS) are 3.6 months and 9.7 months, respectively (Table 3) (Figure 2). Patients who had received previous chemotherapy survived for a median of 13.2 months, compared with 5.0 months for chemo-naïve patients; this difference was not statistically significant (p=0.3117). One year survival was also greater in the previously-treated patients compared with those who were chemo-naïve (57% vs. 30%). As expected, median survival in patients with epithelioid histology was significantly longer than in those with sarcomatoid or mixed histology (10.7 versus 3.7 months p =0.0179) (Table 3, Figure 3).

Biological outcomes

Archival tissue for analysis was available on 42 patients. There were no BRAF mutations detected among these samples. Of the 42 samples, 37 were evaluable for expression of p-ERK 1/2. ERK1/2 phosphorylation could not be evaluated due to insufficient samples in the 3 patients who developed a partial response. Thirty patients were p-ERK 1/2 positive and 7 patients were p-ERK 1/2 negative. Response to treatment (progressive disease, stable disease, inadequately assessed) neither correlated with presence or absence of p-ERK 1/2 (p=0.6745) nor with level of expression of p-ERK1/2 (low versus high) (p=0.1071). Similarly, p-ERK1/2 expression (positive versus negative) had no bearing on either PFS (HR 1.51 95% CI 0.65–3.50, p =0.342) or OS (HR 1.34 95% CI 0.55–3.23, p =0.5211). However, patients with medium or high levels (group 1) had poorer overall survival than those with low or negative (group 2) expression (HR 3.41 95% CI 1.41–8.25, p=0.0066) (Table 4, Figure 4). Because of the small sample size, other factors such as previous treatments, and performance status were unable to be incorporated into the Cox models.

DISCUSSION

Malignant mesothelioma continues to be a therapeutically challenging disease. Outcomes with cytotoxic agents have produced median survivals of about a year or less[1, 13–16]. Given these findings there has been an interest to evaluate novel therapeutic agents in patients with malignant mesothelioma. Angiogenesis is a key event in carcinogenesis and angiogenesis inhibitors have previously been evaluated in mesothelioma. Targeting angiogenesis with a multitude of agents with varied mechanism of action has resulted in response rates of 0–23% and overall survival of 5.9–12.4 months (Table 5). Our current study with single agent sorafenib produced a median survival of 9.7 months and is similar to prior agents targeting this pathway. However, the study failed to meet its primary endpoint. Furthermore, although outcomes appeared to be better in previously treated patients, this likely reflects patient selection as opposed to true clinical activity of sorafenib in this patient population.

The outcome of mesothelioma patients treated with sorafenib was similar to other multi-targeted kinase inhibitors (Table 5). As expected, patients with epitheloid histology fared better than the rest. In a phase II study of sorafenib in hepatocellular carcinoma, high p-ERK 1/2 was associated with improved time to progression than patients with low expression ($p=0.00034$)[17]. These results were mirrored in our study with the finding of improved overall survival in patients with low levels of baseline p-ERK 1/2. This improvement was seen as more than a doubling in overall survival in comparison to those with medium or high levels of expression. Low levels of p-ERK 1/2 may be a reflection of the proliferative state of the cancer. Hence cancers with low levels of p-ERK 1/2 may in general be less aggressive and thus be associated with a better outcome. Although sorafenib inhibits RAF signaling, the current study did not specifically evaluate the effects on p-ERK 1/2 following sorfenib treatment. Furthermore, as sorafenib inhibits angiogenesis, biomarkers such as soluble vascular endothelial growth factor receptor (sVEGFR) or CD31 expression may help define patients likely to benefit from treatment. Additional studies are needed to help further clarify the role of these biomarkers, if any, with sorafenib efficacy.

While several studies with targeted agents in mesothelioma have been to date negative, many important lessons have been learned. First is the issue of patient selection. In most malignancies, response rate and survival decrease with advancing lines therapy. However, such a consistent association in mesothelioma trials is lacking, and median survival of 11–12 months in pretreated patients are seen. This raises the possibility that patients ineligible for cytotoxic chemotherapy due to performance status or other factors, and hence with poorer prognoses are enrolled on front line non-cytotoxic chemotherapy trials thus blunting the effects of targeted therapy in the front line setting. Another important consideration in addition to performance status is the age of patients on mesothelioma trials. Almost half the patients in the current study were ≥ 70 years of age, which is consistent with the median age of diagnosis of mesothelioma (74 years)[18]. This feature has to be accounted for in the design of future trials and mesothelioma trials will need to cater to the elderly.

The heterogeneity within mesothelioma may also confound the results of an investigational agent if evaluated in a single arm study. For example, in a randomized study of cisplatin/gemcitabine with or without bevacizumab, while survival on both arms exceeded the survival in other mesothelioma studies, long term follow up failed to show a benefit with the addition of bevacizumab to chemotherapy (median survival 14.7 months chemotherapy arm, 15.6 months bevacizumab arm, $p=0.91$)[19]. In the absence of the chemotherapy control arm, this study would have led to the spurious conclusion that bevacizumab improves survival with chemotherapy. Hence future studies must strongly consider a randomized phase II design for drug selection. There has been no clear association between response rates and survival; most studies have shown low response rates and often targeted agents do not

typically results in radiologic responses. Recently, multivariate cox regression analyses of 523 patients treated on EORTC (European Organization of Research and Treatment of Cancer) mesothelioma trials led to the development of a performance status, stage, and histology based prognosis index nomogram[20]. This nomogram separated patients into four risk categories with graded progression free survival. Perhaps it is time for a paradigm shift in mesothelioma trials to adopt survival endpoints such as progression free or overall survival as opposed to responses rates.

In conclusion, the current study is another example of an angiogenesis inhibitor with limited activity in mesothelioma. For this class of agents, future trials should include a chemotherapy backbone. Such chemotherapy should be tailored to the elderly and decreased functional status, with endpoints and study design that can adequately reflect the heterogeneity of this disease. Needless to say, therapy for mesothelioma will need to move toward targets beyond angiogenesis. Other likely targets include the proteasome, histone deacetylase, Src, Mesothelin, insulin-like growth factor, and MEK, which are currently being investigated in clinical trials[21–23].

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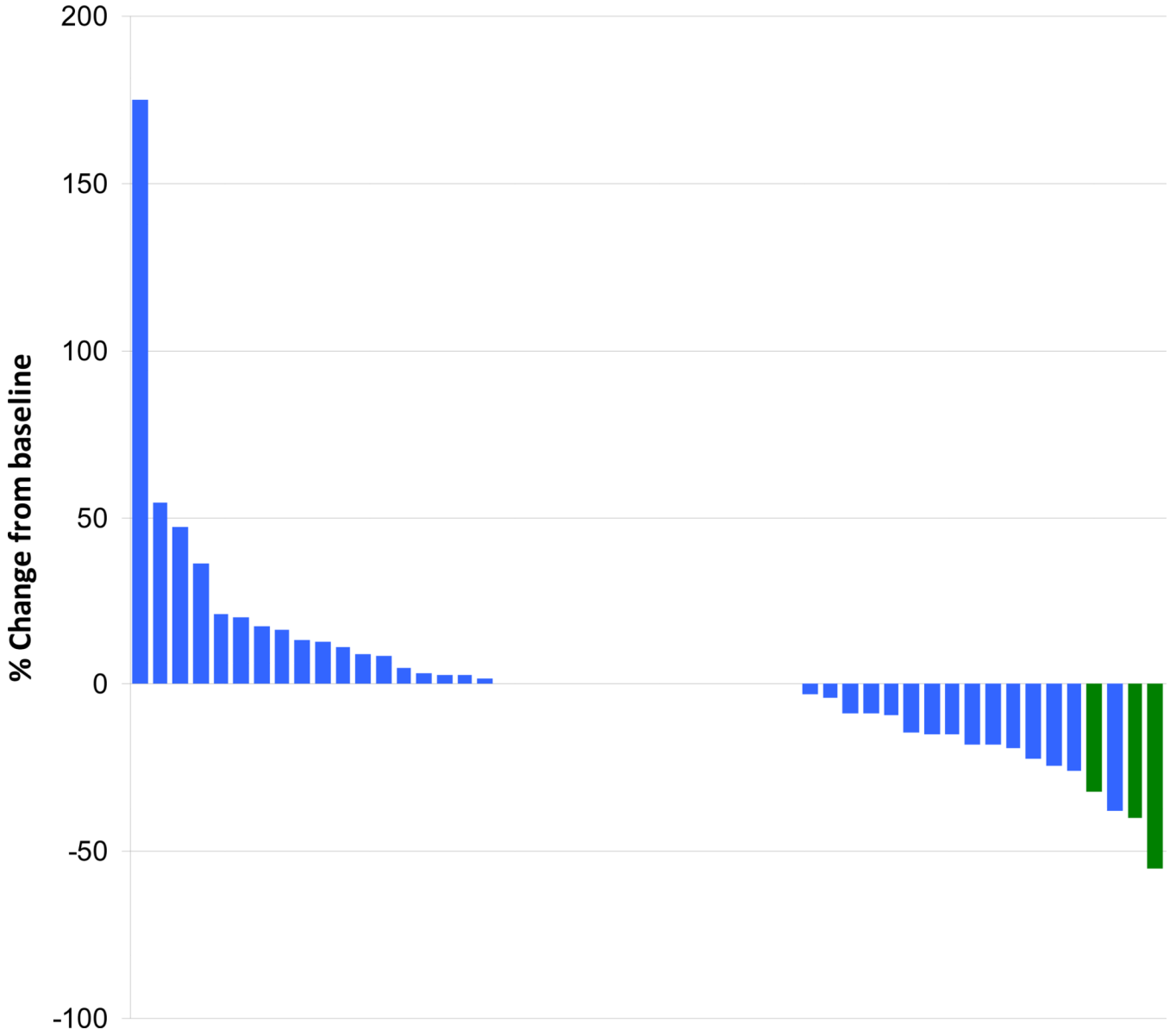

Figure 1. Waterfall plot of Tumor response

Three patients (3%; labeled in green) achieved a partial response with sorafenib treatment.

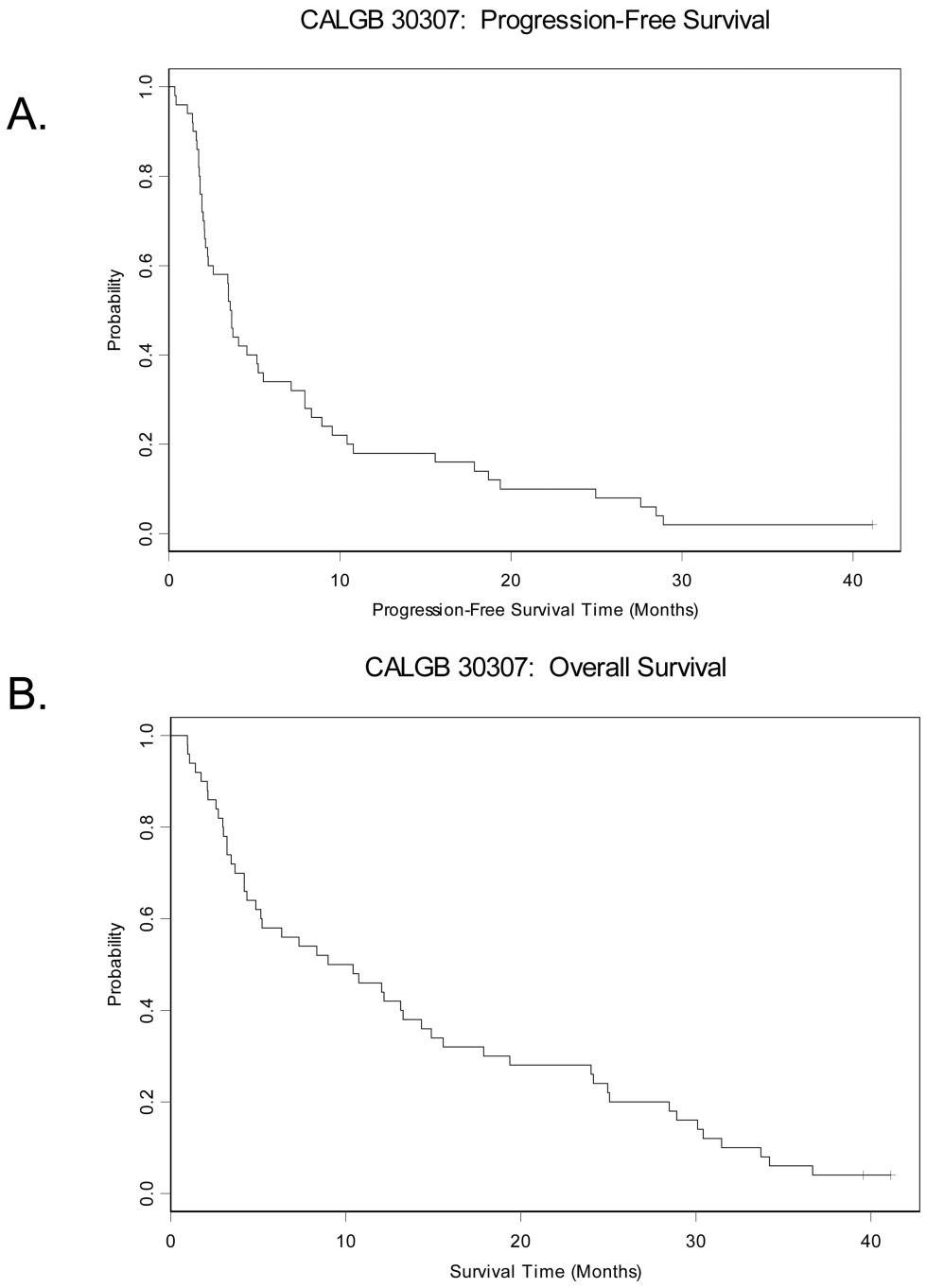

Figure 2. Kaplan-Meier survival curves for progression free and overall survivals

A. Median progression-free survival was 3.6 months with 18% 1-year progression free survival. **B**. Median overall survival was 9.7 months with 46% 1-year survival.

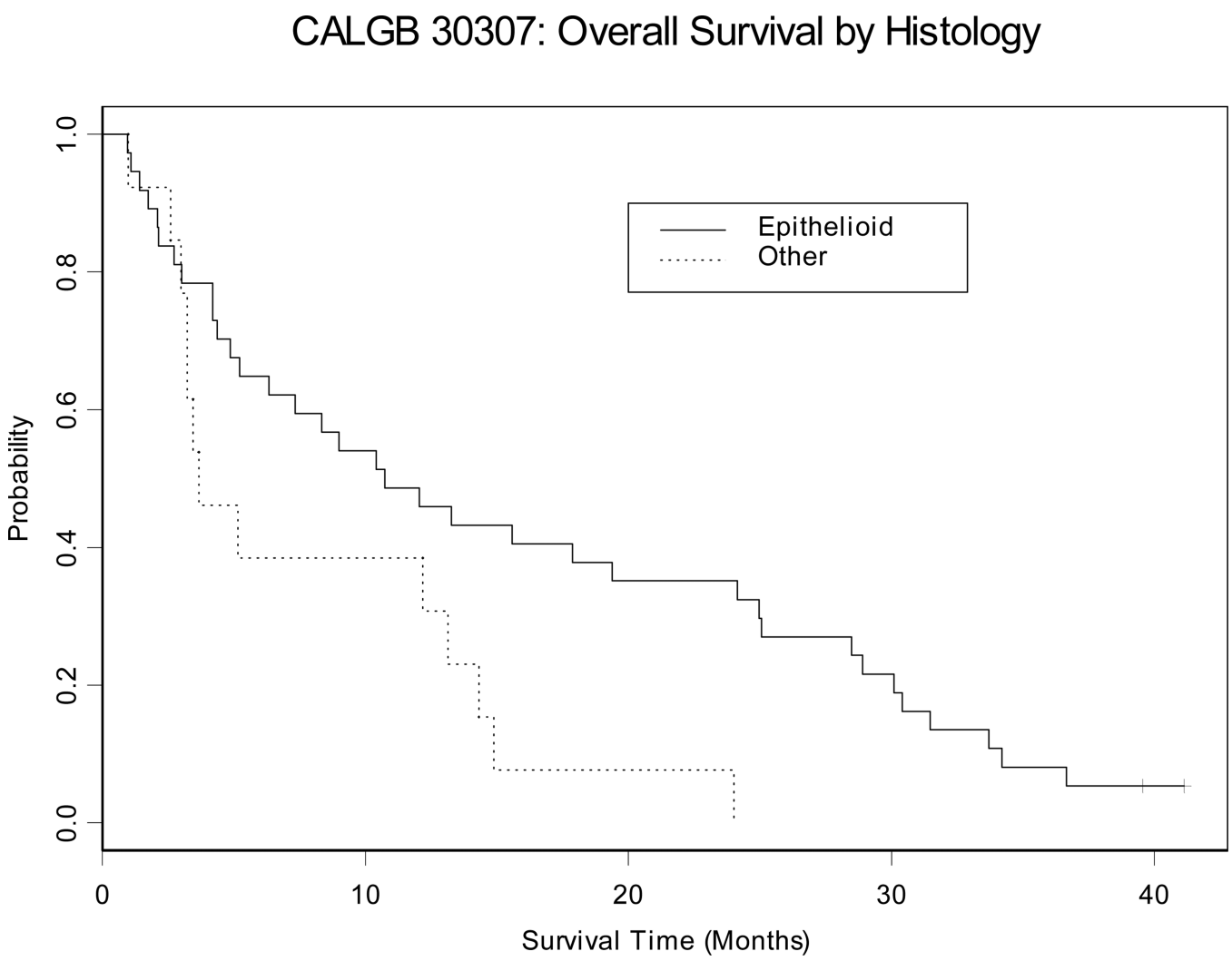

Figure 3. Kaplan-Meier Survival Curves for Overall Survival by histology
Median overall survival was higher with epithelioid histology than others (10.7 vs 3.7 months months, p=0.0179).

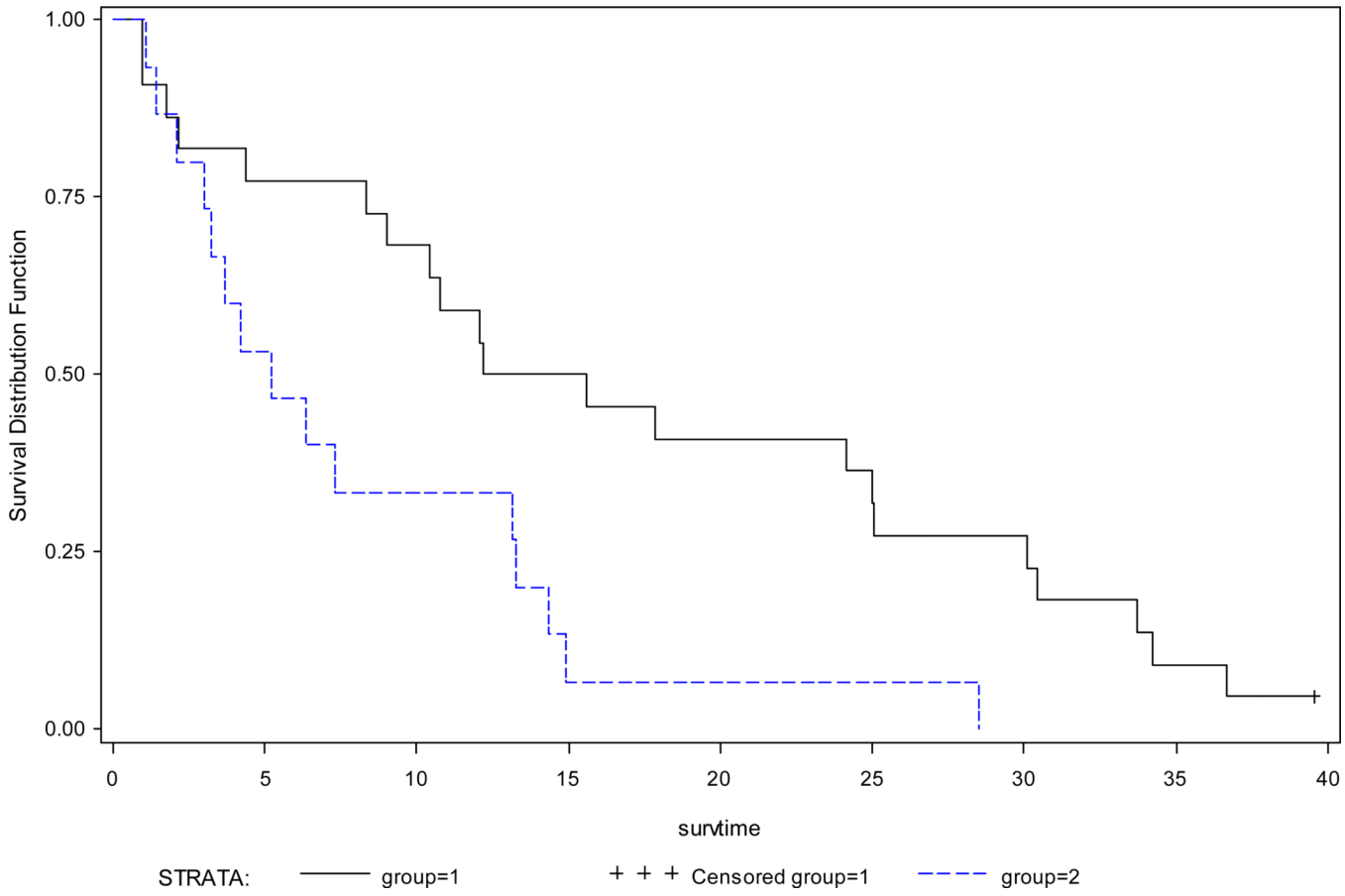

Figure 4. Kaplan Meier survival curves for overall survival time by p-ERK expression

High baseline pERK 1/2 expression is associated with poorer overall survival. Median survivals were 5.2 months for medium/high expression (blue; group 1) and 13.9 months negative / low expression groups (black; group 2); p=0.0066.

Table 1

Patient Demographic and Clinical Characteristics (N=50)

Characteristics		N	(%)
Gender	Male	35	(70%)
	Female	15	(30%)
Age	< 50	3	(6%)
Median: 69	50 – 59	8	(16%)
Range (36,88)	60 – 69	17	(34%)
	70+	22	(44%)
Mesothelioma	Epithelioid	37	(74%)
Histology	Sarcomatoid	4	(8%)
	Mixed	7	(14%)
	Subtype		
	Unknown	2	(4%)
Site of Origin	Pleura	45	(90%)
	Peritoneum	5	(10%)
Previous	Yes	30	(60%)
Chemo	No	20	(40%)
Performance	0	11	(22%)
Status	1	39	(78%)

Table 2

NCI CTC grade 3 and 4 toxicities following sorafenib treatment

Toxicity	N = 50	
	Grade 3 N (%)	Grade 4 N (%)
HEMATOLOGICAL		
Lymphopenia	2 (4%)	0
Hemoglobin	1 (2%)	0
Hemolysis	1 (2%)	0
NON-HEMATOLOGICAL		
Fatigue	12 (24%)	1 (2%)
Rash: hand-foot skin reaction	6 (12%)	0
Dyspnea (shortness of breath)	4 (8%)	0
Pain	3 (6%)	0
Anorexia	2 (4%)	0
Neuropathy: sensory	2 (4%)	0
Hypertension	2 (4%)	0
Hypotension	1 (2%)	0

Table 3

Progression free and overall survivals based on prior chemotherapy treatment and histology.

		Overall Survival			Progression Free survival		
		Median in months (95% CI)	**1-year Survival (95% CI)**	**p value**	**Median in months (95% CI)**	**3-month Survival (95% CI)**	**p value**
Overall Population	N=50	9.7 (4.4, 14.3)	46% (31.9, 59)		3.6 (2.3, 5.5)	58.0 % (43.2, 70.2)	
Prior Chemotherapy	Chemo naive N=20	5.0 (3.0, 12.2)	30% (12.3, 50)	0.3117	2.9 (1.9, 5.5)	50.0 (27.1, 69.2)	0.3181
	Prior chemo N=30	13.2 (5.2, 19.4)	56.7% (37.3, 72.1)		3.7 (2.3, 8.9)	63.3 % (43.6, 77.8)	
Histology	Epithelioid N= 37	10.7 (5.2,24.1)	48.6 % (32.0, 63.4)	0.0179	4.1 (2.1, 8.0)	59.5 % (42.0, 73.2)	0.1034
	Other N=13	3.7 (3.0, 13.1)	38.5 % (14.1, 62.8)		3.4 (1.9, 3.7)	53.9 % (24.8, 76.0)	

Table 4

Progression free and overall survivals based on p-ERK 1/2 expression

	N	Median (months)	HR (95% CI)	P value
Progression Free Survival				
pERK (negative/low)	22	6.7		
pERK (medium/high)	15	2.1	2.15 (0.94–4.90)	0.0701
Overall Survival				
pERK (negative /low)	22	13.9		
pERK (medium/high)	15	5.2	3.41 (1.41–8.25)	0.0066

Table 5

Phase II studies of anti-angiogenic agents in mesothelioma.

Drug	Line of therapy	Response	SD	TTP / PFS months	Median OS months
Vatalanib[24]	1st line	8%	72%		10
Thalidomide[25]	1st and 2nd line	0%	28%		7.5
SU5416[26]	2nd line	11%	38%	2 (TTP)	12.4
Thalidomide[27]	2nd line	6%	50%	8 weeks (TTP)	11
Sunitinib[28]	2nd line	23%		3.5 (TTP)	5.9
AZD2171[29]	2nd line	9%	33%	3 (PFS)	10
Sorafenib (Current study)	***1st and 2nd line***	***6%***	***54%***	***3.6(PFS)***	***9.7***

SD; stable disease, TTP; Time To Progression, OS; overall survival, PFS; Progression free survival