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Phase II Trial of Carboplatin, Paclitaxel, Cetuximab and Bevacizumab Followed by Cetuximab and Bevacizumab in Advanced Non-Squamous Non-Small Cell Lung Cancer: SWOG S0536

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Abstract

Introduction—Cetuximab and bevacizumab have each been demonstrated to prolong survival when added to chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). However, the potential benefit of combining cetuximab and bevacizumab together with a platinum-based doublet had not been explored. We designed this phase II trial to evaluate the safety, tolerability and efficacy of the combination of carboplatin, paclitaxel, cetuximab and bevacizumab in chemotherapy-naïve patients with advanced, non-squamous NSCLC.

Methods—Patients received with up to six cycles of carboplatin (area under curve 6), paclitaxel (200 mg/m^2), cetuximab (400 mg/m^2 day 1 then 250 mg/m^2 weekly) and bevacizumab (15 mg/kg) every 21 days. Patients with an objective response or stable disease received maintenance cetuximab (250 mg/m^2 weekly) and bevacizumab (15 mg/kg every 21 days) until disease progression. The primary endpoint was safety as defined by the frequency and severity of hemorrhagic toxicities. Secondary endpoints included response rate (RR), progression-free

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Results presented in part by Dr. Edward Kim at the Annual Meeting of the International Association for the Study of Lung Cancer, July 31-August 4, 2009, San Francisco, CA; Annual Meeting of the International Association for the Study of Lung Cancer, April 23-26, 2008, Geneva, Switzerland; and by Drs. David Gandara, Philip Mack and Wilbur A. Franklin (individual presentations) at the Annual Meeting of the American Society of Clinical Oncology, May 29-June 2, 2009, Orlando, FL

survival (PFS), overall survival (OS), and toxicity. Molecular biomarkers were assessed in an exploratory manner.

Results—The primary endpoint of grade 4 or higher hemorrhage of 2% (95% confidence interval: 0-7%) met prespecified criteria for safety. Oone hundred ten patients were enrolled. There were 4 treatment-related deaths including lung hemorrhage (2), infection (1), and unknown (1). Median progression-free survival was 7 months and median overall survival was 15 months. The RR was 56% with an overall disease control rate of 77%.

Conclusion—This regimen was safe, feasible and effective as frontline treatment of advanced NSCLC, providing the basis for the ongoing Phase III trial S0819.

Keywords

Non-small-cell lung cancer; Paclitaxel; Carboplatin; Cetuximab; Bevacizumab; Frontline

INTRODUCTION

Progress in chemotherapy-based treatment of non-small cell lung cancer (NSCLC) has been slow. Front-line treatment has consisted of platinum-based doublets; typically producing median survivals of 8 to 10 months.[1] Efforts to combine novel targeted agents with chemotherapy have been largely unsuccessful in the majority of trials, partly due to failure to account for the complex biology intrinsic to human lung cancers. [2-3] An individual patient's cancer, for example, may be dependent on multiple growth pathways, including vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). Thus, investigating combinations of targeted agents against these pathways is warranted.

Bevacizumab, a monoclonal, recombinant, humanized, murine antibody that targets VEGF, has been demonstrated to prolong overall survival (OS) when added to carboplatin and paclitaxel for chemotherapy-naïve patients with non-squamous NSCLC [4] in the E4599 study. In this randomized phase III trial, of carboplatin and paclitaxel with or without bevacizumab in patients with chemotherapy-naïve, recurrent or metastatic, non-squamous NSCLC, median progression-free survival (PFS) and OS increased from 4.5 and 10.3 months in the chemotherapy alone arm, respectively, to 6.2 and 12.3 months in the chemotherapy plus bevacizumab arm ($p<0.05$ for both). The FDA approved the bevacizumab NSCLC combination in October, 2006.

Cetuximab, a chimerized immunoglobulin G1 antibody, blocks ligand-induced EGFR activation and has shown activity in multiple cancers including NSCLC. The phase III First Line Erbitux (FLEX) study of cisplatin and vinorelbine with or without cetuximab demonstrated increased OS in the cetuximab arm in patients with advanced EGFR-positive NSCLC. [5] In contrast, BMS 099, a phase III trial of chemotherapy with or without cetuximab in patients not preselected for EGFR status, failed to meet the primary endpoint of improved PFS, despite a numerically higher response rate (RR) and longer survival.[6] Our predecessor trial SWOG 0342, a phase II trial of cetuximab with carboplatin and paclitaxel in advanced NSCLC patients, demonstrated tolerability and identified EGFR gene copy number as a potential predictive biomarker of efficacy.[7] Combination regimens targeting

EGFR and VEGF pathways have been investigated in other tumor types with mixed success.[8-10] In NSCLC, trials employing EGFR tyrosine kinase inhibitors plus bevacizumab have shown improvements in PFS, but have failed to demonstrate statistically improved OS.[11,12]

Our study, SWOG 0536, (ClinicalTtrials.gov Identifier: NCT00368992 http://clinicaltrials.gov/) sought to assess the safety, feasibility and efficacy of a novel four drug regimen, combining a chemotherapy doublet with a biologic doublet, in advanced NSCLC patients. We also explored the relationship between potential predictive biomarkers for the EGFR and VEGF pathways and clinical outcomes.

PATIENT AND METHODS

Patient Eligibility

Patients had histologically confirmed, advanced stage IIIB or IV non-squamous NSCLC appropriate for frontline cytotoxic treatment and bevacizumab. Patients with squamous cell carcinoma or brain metastases were ineligible. Patients must not have received any prior systemic NSCLC therapy (biologic, adjuvant) Patients must not have received prior EGFR or VEGF pathway agents, chimerized or murine monoclonal antibody therapy, or have documented presence of human anti-mouse antibodies. Prior radiation therapy and surgery were allowed. Patients must have normal organ function, a Zubrod performance status of 0-1, and age 18 years or more. Patients with any condition that carried a high risk of bleeding or with any non-healing wound, ulcer or bone fracture were ineligible.

The protocol was approved by the institutional review boards at participating institutions. Patients were informed of the investigational nature of the study and provided written informed consent in accordance with institutional and federal guidelines, including the banking of tumor, whole blood and serum specimens to explore relevant molecular parameters.

Treatment Plan

Patients received a loading dose of Cetuximab 400 mg/m^2 IV on day 1. One week later, patients received Cetuximab 250 mg/m^2 IV, paclitaxel 200 mg/m^2 IV, carboplatin (area under the curve [AUC] of 6) IV, and bevacizumab 15 mg/kg IV. Carboplatin, paclitaxel, and bevacizumab were administered every 3 weeks with cetuximab weekly. Cycles were repeated every 21 days for a maximum of six cycles. Patients with an objective response or stable disease received maintenance cetuximab (250 mg/m^2 weekly) and bevacizumab (15 mg/kg every 21 days) until disease progression, death, or intolerable toxicity.

Dose Modifications

Chemotherapy (i.e., carboplatin and paclitaxel) delays, dose reductions and discontinuation were implemented according to standard criteria pre-specified in the protocol according to the National Cancer Institute Common Terminology Criteria of Adverse Events (version 3.0). For bevacizumab: dose reductions were not allowed; administration was delayed for Grade 3 toxicities (non-pulmonary hemorrhage, congestive heart failure, proteinuria) and

Grade ≥ 2 bowel obstruction; permanently discontinuation for Grade 3-4 hypertension. Patients who required a treatment delay of 4 weeks or more were not permitted to restart bevacizumab. Cetuximab dose reductions were infusion reactions, hypomagnesemia, and dermatologic or pulmonary toxicities. Grade 3 and 4 infusion reactions required discontinuation of cetuximab or bevacizumab.

Evaluations

All patients had baseline evaluation with history and physical examination, serum chemistry and hematologic tests, and imaging studies for assessment of disease status. Blood count, electrolytes, magnesium and liver function tests were obtained prior to each cycle. Proteinuria (urine protein creatinine ratio or dipstick urinalysis) was monitored every 2 cycles. Imaging studies for assessment of treatment response were also obtained every 2 cycles. Tumor response by RECIST criteria was assessed every two cycles.[13]

Study Endpoints and Statistical Analysis

The primary endpoint of the study was to evaluate the frequency and severity of hemorrhage-related toxicities, as defined by Common Terminology Criteria of Adverse Events. It was assumed if the true rate of Grade 4-5 hemorrhage-related toxicities was 10% or higher then this regimen would present an unacceptably high risk for further study. However, if the true rate were 3% or less then the risk of hemorrhage would be acceptable and the regimen would warrant further investigation, provided PFS, OS, and non-hemorrhage-related toxicities also appeared favorable.

The planned sample size was 90 evaluable patients to be enrolled over five months. If five or more patients experienced Grade 4-5 hemorrhage at any point, the trial would be closed with the conclusion that the frequency of Grade 4-5 hemorrhage toxicities was too high to warrant further study of the regimen. This design had 87% power using a one-sided exact test based on the binomial distribution with a significance level of 5%. In addition, assuming 12 months of follow-up, this design would also have 82% power, (using a test of medians with a one-sided [alpha] of 0.05) to rule out the null hypothesis of an 8-month median survival versus an alternative of a 12-month median survival. An observed median survival of 10 months or longer would be considered evidence that this regimen warrants further testing provided this regimen is considered safe based on the outcome of the primary study objective.

Other secondary endpoints included PFS, RR (confirmed plus unconfirmed, complete plus partial) in the subset of patients with measurable disease at baseline (Response Evaluation Criteria in Solid Tumors), and the overall toxicity profile. Ninety patients would allow for the estimation of RR and toxicity rates to within ± 11% (95% confidence interval). Any toxicity occurring with at least 5% probability was highly likely to be seen at least once (99%).

All eligible patients who received at least one dose of the study drug were analyzed for efficacy and toxicity endpoints. Continuous variables are presented using median (range), with any comparisons made using either the t-test or Wilcoxon rank-sum test, depending on the observed distribution. Categorical variables are summarized in frequency tables, with

any comparisons made using Fisher's exact test. OS and PFS estimates were computed using the method of Kaplan and Meier[14] and confidence intervals for the medians were constructed using the method of Brookmeyer and Crowley[15].

Biomarker Studies

Correlative analyses were performed to explore associations between clinical outcomes and tumor-associated EGFR pathways biomarkers (mutational status, gene copy number, protein expression) and KRAS mutation status, including identification of potential cut points in marker levels to guide correlative studies in future trials. Cox regression techniques[16] were used to assess the associations between markers and OS and PFS. Fisher's Exact test was used to assess the association with RR and disease control rate (DCR). In addition, the association between clinical outcomes and a selected subset of 35 plasma circulating cytokine-angiogenesis factors (CAF) were explored. We investigated baseline levels of these markers and the percent change between baseline and levels at Week 5 of treatment. Raw data were converted to ranks and the ranks were transformed into a percentile between 0 and 1. Cox regression was used to investigate PFS and OS, and logistic regression was used to evaluate RR and DCR. As these analyses were for exploratory purposes, unadjusted *p* values are provided.

RESULTS

Between August 2006 and September 2007, 110 patients were enrolled in the study (Fig. 1). Five patients were ineligible: 3 who had squamous cell histology, and 2 who did not have the correct stage. Three eligible patients refused protocol treatment and were not analyzable for any of the study endpoints, leaving 102 evaluable patients. Table 1 shows baseline patient characteristics.

Toxicity Results

The primary endpoint of grade 4 or higher hemorrhage was 2% (95% CI: 0-7%). Both patients had grade 5 pulmonary hemorrhage. There were 2 additional treatment-related deaths: one from infection and one with cause of death unknown. Overall toxicities were acceptable and comparable to reference trials S0342 and E4599[7,4]. A summary of selected Grade 3-5 toxicities is presented in Table 2. The most common adverse events (grad >=3) were acneiform rash, neutropenia, infection, neuropathy, and fatigue.

Efficacy Results

In ninety-five patients with measurable disease the overall RR was 56% (52/95; 44% - 65%). Overall DCR was 77% (stable disease 21/95 (22%). The estimated median PFS was 7 months (95% CI: 6-8 months) and median OS was 15 months (95% CI: 11-21 months). One- year survival is 57%; (95% CI: 47%-66%) (Fig. 2). The median follow up time among the 17 patients still alive is 42 months (range: 32-51 months).

Treatment Delivery

The median number of cycles received during cycles 1 to6 was 4 (range 1-6). Forty-seven patients (46%) went on to receive maintenance treatment. The median number of maintenance cycles received was 12 (range 7-47).

Biomarker Results

Analyzable tumor specimens were available from 66 patients for one or more correlative science studies, prioritized in the following order: EGFR gene copy number, by fluorescent in situ hybridization (FISH), KRAS mutation, EGFR mutation and EGFR protein by expression by immunohistochemistry. Tumor specimens were classified as EGFR FISH positive if there were 4 or more gene copies per cell in at least 40% of the cells (high polysomy) or gene amplification. Results from the correlative analysis of biomarkers and clinical outcomes are presented in Table 3. EGFR FISH was assessable in 50 patients, and 26 (52%) were EGFR FISH positive (20 high polysomy, 6 gene amplification). Although the RR and DCR were numerically higher in EGFR FISH positive cancers (64% versus 45% and 88% versus 73%), these differences were not statistically significant (RR: p=0.25; DCR: p=0.27). EGFR FISH-positivity was not significantly associated with other clinical outcomes (PFS: p=0.91; OS: p=0.13) (Fig. 3A).

KRAS mutation status was assessable in 32 patients and 28% harbored KRAS mutations. No statistically significant associations were observed between KRAS mutation status and clinical outcomes (RR: p=1.00; DCR: p=1.00; PFS: p=0.27; OS p=0.49; Fig. 4), although similar to our prior observation in S0342, patients with KRAS mutation had numerically longer PFS and OS.

EGFR mutation status was assessable in 31 patients and 16% harbored EGFR mutations. No statistically significant associations were observed between EGFR mutation status and clinical outcomes (RR: p=1.00; DCR: p=0.27; PFS: p=0.11; OS: p=0.41).

EGFR protein expression by immunohistochemistry was assessable in 64 patients. The median H Score was 150 (range: 0-300). Four different dichotomous cut points were analyzed: H score 0 (47 patients) vs. 0 or higher (17 patients), 100 or more (35 patients) versus less than 100 (29 patients), 200 or more (23 patients) vs. <less than 200 (41 patients), and H-score = 300 (10) vs. less than 300 (54 patients). Although high H scores trended toward better RR, PFS and OS, there were no statistically significant associations between clinical outcomes for any of the four cut points.

The association between plasma levels of circulating CAF and clinical outcomes was investigated. Plasma samples were available from 74 patients. In this exploratory analysis, higher baseline levels of Hu PDGF-bb (47) were associated with better PFS (p=0.03). Higher baseline levels of Hu hepatocyte growth factor (HGF) (62) ($p < 0.01$), matrix metalloproteinase-9 (27) (p=0.04), and osteopontin (p=0.02) were associated with worse OS. Higher baseline levels of Hu HGF (62) ($p = 0.03$), matrix metalloproteinase-9 (27) (p=0.049), HU interleukin (IL)-18 (42) (p=0.01), Hu stem cell growth factor(SCGF-b) (78), and HU VEGF (45) were associated with a worse DCR, while a high baseline level of sVEGFR2 was associated with a better DCR. Increased levels over baseline at week 5 of

HU monocyte chemotactic protein (MCP)-3- (26) (p=0.04) and HU TNF-related apoptosis-inducing ligand (TRAIL) (66) (p=0.04) were associated with worse PFS. Increases in Hu granulocyte-macrophage colony-stimulating factor (GM-CSF) (34) (p=0.03), Hu interferon (IFN)-g (21) (p=0.02), Hu macrophage inflammatory protein (MIP)-1a (55) (p=0.01) and Hu platelet-derived growth factor (PDGF)-bb (47) (p=0.01) were associated with worse OS, while increases in osteopontin (p =0.01) and CA-9 (p=0.04) were associated with better OS. An increase over baseline in the level of Hu G-CSF (57) was associated with a higher RR. Increases in Hu IL-16 (27), Hu IL-18 (42), Hu IL-9 (77), and Hu MCP-1(MCAF) were associated with a higher DCR.

Finally, clinical outcomes and selected baseline characteristics were compared between patients with assessable specimens (tissue or blood, n=84) versus those in which specimens were not assessable (n=18) (Table 4); Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/JTO/A484). There was no significant difference in performance status (p=1.00), sex (0.44), race (white vs. all other;) p=0.69), histology (adenocarcinoma versus. all others) (p=0.52), smoking status (never versus. current/former; p=0.35), tumor, node, metastasis stage (p=0.35), OS (HR: submitted specimen vs. none: = 0.66, 95% CI: 0.38-1.13; p=0.13), RR (p=0.78, or DCR (p=0.18). However, patients who submitted specimens had a significantly better PFS (HR=0.59, 95% CI: 0.35-1.00; p=0.047).

DISCUSSION

SWOG S0536 is the first study to evaluate the combination of platinum-based chemotherapy plus cetuximab and bevacizumab in patients with advanced stage NSCLC. Using the E4599 and S0342 trials[4, 7] as reference regimens, the four-drug S0536 regimen was not associated with excess toxicity, notably pulmonary hemorrhage. Bleeding (including hemoptysis) has been associated with bevacizumab treatment for NSCLC, even in patients with non-squamous histology. In E4599, grade 3 or more bleeding occurred in 22 out of 427 bevacizumab-treated patients (5.2%), with hemoptysis occurring in eight patients (1.9%).[4] In AVAiL, bleeding of grade 3 or more occurred in 28 out of 659 bevacizumab-treated patients (4.2%), with hemoptysis in eight patients (1.2%).[17]

Further, we observed efficacy outcomes warranting further study, with a response rate of 54%, PFS of 7 months and OS of 15 months. These phase II efficacy results compare favorably with other experiences with triplet regimens based on cetuximab or bevacizumab, including E4599, AVAiL, FLEX, BMS 099, and S0342[4, 4-7, 17]. The p;ercdrntage of patients who completed induction chemotherapy and went on to maintenance treatment was 46%. This compares with 60% in the E4599 and 42% in AVAiL. The OS and PFS observed in E4599 for the bevacizumab-containing arm were 12.3 months and 6.2 months, and in AVAIL were 13.4 months (bevacizumab 7.5 mg/kg) and 13.6 months (bevacizumab 15 mg/kg), and 6.5 months (bevacizumab 7.5 mg/kg) and 6.7 months (bevacizumab 15 mg/kg), respectively.

The FLEX study, a large trial of over 1000 patients, demonstrated an OS (primary endpoint) improvement of 11.3 versus 10.1 months [5]. In comparison, the smaller BMS 099 study[6]

showed no benefit in PFS (primary endpoint) despite improved RR and OS (9.7 versus 8.4 months).

Our predecessor phase II SWOG study S0342, which tested a combination of carboplatin, paclitaxel and cetuximab in two different schedules (concurrent or sequential) reported OS (10.7 and 10.9 months) and PFS (4.3 and 4.4), respectively.[6] S0536 built upon this S0342 platform by adding bevacizumab, based on benefits seen for bevacizumab in E4599 and AVAiL, plus data supporting combined VEGF-EGFR-directed therapy.

Results of clinical trials combining EGFR and VEGF blockade have shown mixed results and may be tumor type-specific. In two recently reported colorectal cancer studies, the addition of cetuximab and bevacizumab to existing chemotherapy regimens failed to demonstrate benefit. One study randomized 755 patients with previously untreated metastatic colorectal cancer to capecitabine, oxaliplatin, and bevacizumab with or without cetuximab for metastatic colorectal cancer.[8] Another study randomized over 1000 patients to receive chemotherapy (oxalipatin or irinotecan-based) with bevacizumab with or without panitumumab, a fully human antibody targeting the EGFR.[9] In both studies, PFS was lower and toxicity increased in the EGFR antibody-containing arm. Combinations of erlotinib with bevacizumab in phase III trials have been more promising (Bevacizumab and Tarceva [BeTa], Avastin and Tarceva in Lung with Lung Cancer [ATLAS].[11-12]

The currently ongoing S0819 is designed to directly test the hypothesis of combined EGFR-VEGF blockade together with chemotherapy. This phase III biomarker validation study compares carboplatin-paclitaxel with or without cetuximab, and allows inclusion of bevacizumab in both arms, based on previously reported bevacizumab eligibiity criteria (E4599). S0819 incorporates EGFR FISH as a co-primary endpoint, based on our previous observations from S0342 that EGFR FISH-positive patients demonstrated improved response, PFS and OS with paclitaxel-carboplatin-cetuximab. S0536 also explored a variety of potential prognostic and/or predictive biomarkers, with particular attention to whether the addition of bevacizumab would alter previously described associations from other cetuximab-based studies such as S0342 or FLEX. In S0536, although FISH-positive patients had a trend for higher RR and DCR, outcome differences were not statistically significant. This difference may merely reflect the exploratory nature of these observations in serial Phase II studies and the retrospective nature of the H score observation from FLEX. Regardless, the S0819 Phase III trial is designed to account for a bevacizumab effect within the statistical design. Based on the S0536 observations described here, additional biomarkers such as EGFR protein H score and CAF profiling are being evaluated in the Phase III S0819 study as well. Finally, KRAS mutation status was not associated with a detrimental effect on efficacy parameters in S0536, mimicking our S0342 results as well as those from retrospective analyses of FLEX and BMS099, and in contrast to reports from multiple trials of cetuximab-based therapy in colorectal cancer.[18,19]

In conclusion, S0536, the first reported study to combine carboplatin, paclitaxel, cetuximab and bevacizumab, demonstrates that the regimen is safe, feasible and efficacious as first-line treatment for advanced non-squamous, non-small cell lung cancer. Further evaluation of this regimen is ongoing in the Phase III trial S0819.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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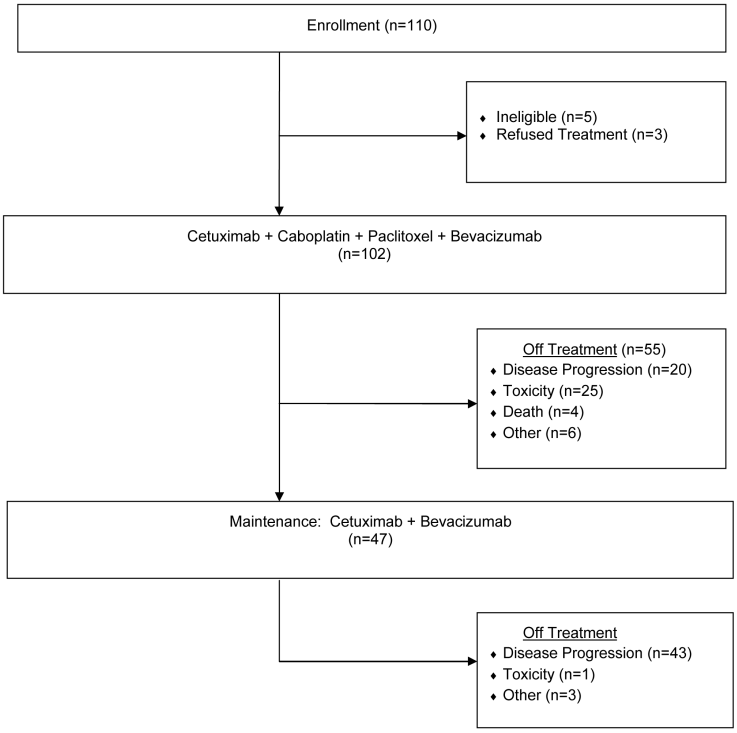

Figure 1.
CONSORT diagram

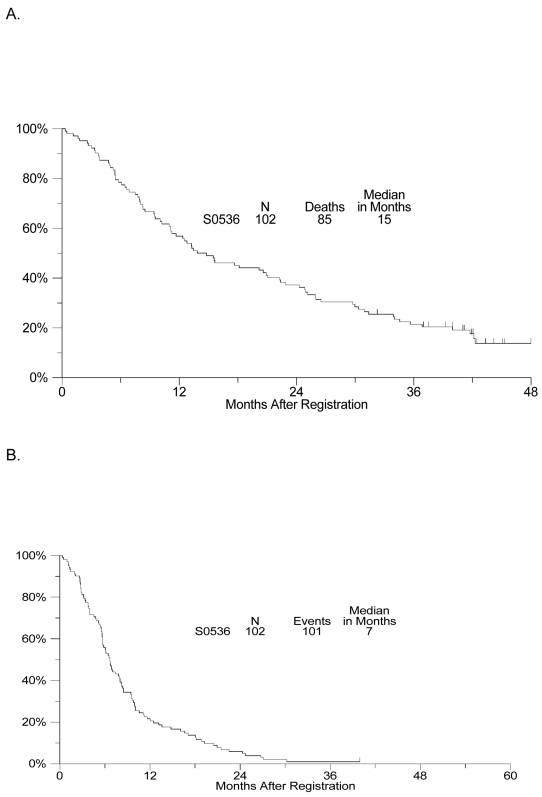

Figure 2.
Kaplan-Meier curves for progression-free survival (A) and overall survival (B).

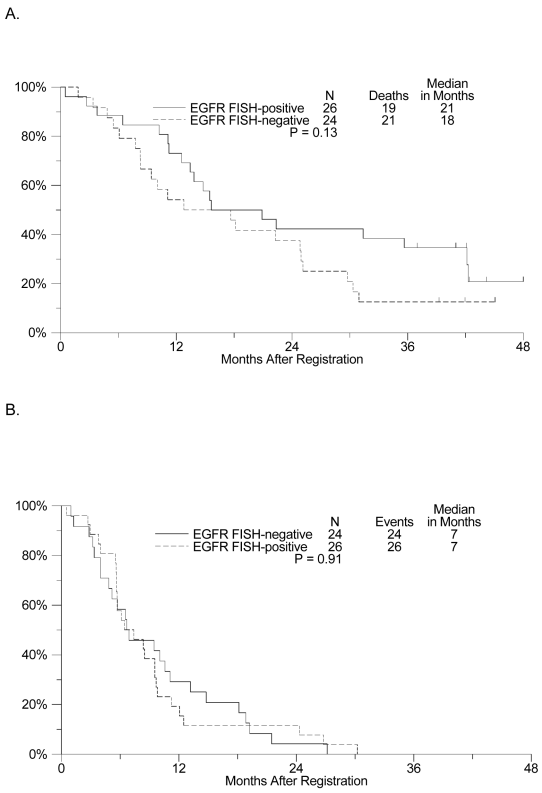

Figure 3.

Progression free survival (A) and overall survival (B) by EGFR FISH status. EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization.

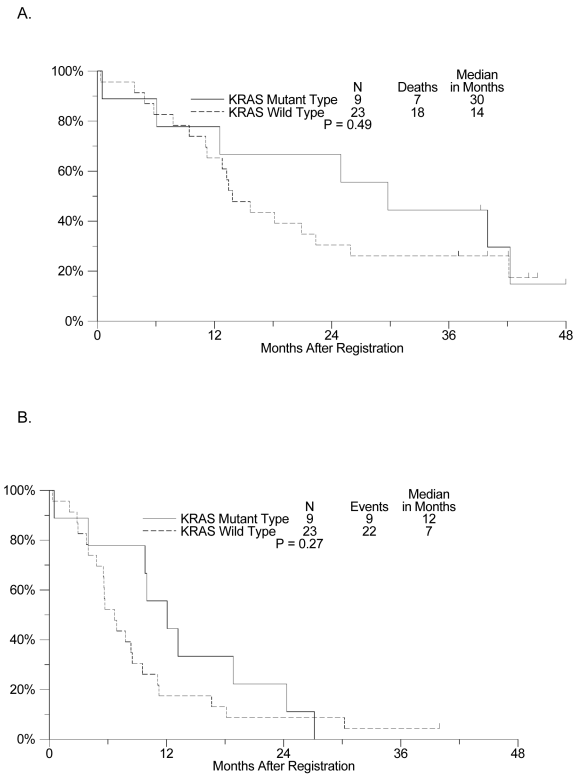

Figure 4.

Progression free survival (A) and overall survival (B) by KRAS mutation status.

Table 1

Baseline patient characteristics

Characteristic	Number of patients (%) N=102
Median age, years (range)	64 (42-78)
Performance status	
0	42 (41%)
1	60 (59%)
Sex	
Female	50 (49%)
Male	52 (51%)
Ethnicity	
White	89 (87%)
African-American	6 (6%)
Asian/Pacific Islander	3 (3%)
Other	4 (4%)
Smoking status	
Never smoker	22 (22%)
Former / current smoker	80 (78%)
Histology	
Adenocarcinoma	81 (79%)
Other	21 (21%)
Stage	
IIIB	7 (7%)
IV	95 (93%)
Weight loss (last 6 months)	
<5%	69 (68%)
5 to <10%	18 (18%)
10-20%	13 (13%)
>20%	1 (1%)
Not Reported	1 (1%)

Table 2

Selected Grade 3-5 Adverse Events

	Grade 3		Grade 4		Grade 5		Total	
Hematologic								
Febrile neutropenia	5	5%	1	1%	0	0%	6	6%
Hemoglobin	3	3%	0	0%	0	0%	3	3%
Neutrophils	23	23%	27	26%	0	0%	50	49%
Platelets	3	3%	1	1%	0	0%	4	4%
Nonhematologic								
Allergic reaction	7	7%	0	0%	0	0%	7	7%
Death, NOS	0	0%	0	0%	1	1%	1	1%
Dehydration	5	5%	1	1%	0	0%	6	6%
Dermatologic/Skin	27	26%	0	0%	0	0%	27	26%
Diarrhea	5	5%	0	0%	0	0%	5	5%
Dyspnea	7	7%	2	2%	0	0%	9	9%
Fatigue	17	17%	2	2%	0	0%	19	19%
GI Perforation: colon	1	1%	0	0%	0	0%	1	1%
Hypertension	2	2%	0	0%	0	0%	2	2%
Hypokalemia	6	6%	1	1%	0	0%	7	7%
Hypomagnesemia	3	3%	2	2%	0	0%	5	5%
Infection	12	12%	1	1%	1	1%	14	14%
Lung Hemorrhage	1	1%	0	0%	2	2%	3	3%
Nausea/Vomiting	8	8%	0	0%	0	0%	8	8%
Neuropathy-motor/sensory	15	15%	2	2%	0	0%	17	17%
Proteinuria	1	1%	0	0%	0	0%	1	1%
Thrombosis/embolism	2	2%	7	7%	0	0%	9	9%

NOS, not otherwise specified; GI, gastrointestinal.

Table 3

Results of Biomarker Analysis

Biomarker	PFS Hazard Ratio	95% CI	*p*	OS Hazard Ratio	95% CI	*p*
KRAS mutation	0.64	0.29-1.42	0.27	0.74	0.30-1.78	0.49
EGFR mutation	2.35	0.83-6.65	0.11	0.60	0.18-2.03	0.41
EGFR FISH positive	1.03	0.59-1.82	0.91	0.61	0.33-1.15	0.13
High polysomy	0.94	0.52-1.68	0.83	0.69	0.36-1.33	0.27
Gene amplification	1.26	0.53-3.02	0.60	0.76	0.29-1.99	0.58
EGFR IHC > 0	0.90	0.51-1.57	0.70	0.63	0.34-1.15	0.13
EGFR IHC ≥ 100	0.71	0.43-1.19	0.19	0.62	0.36-1.08	0.09
EGFR IHC ≥ 200	0.70	0.42-1.19	0.19	0.88	0.50-1.55	0.65
EGFR IHC = 300	0.53	0.26-1.08	0.08	0.54	0.24-1.21	0.14

Biomarker	RR	*p*	DCR	*p*
KRAS mutation	57%	1.00	86%	1.00
KRAS wild type	52%		78%	
EGFR mutation	60%	1.00	60%	0.27
EGFR wild type	54%		83%	
EGFR FISH-positive	64%	0.25	88%	0.27
EGFR FISH-negative	45%		73%	
EGFR FISH high polysomy	58%	1.00	89%	0.28
None	54%		75%	
EGFR FISH gene amplification	83%	0.20	83%	1.00
None	51%		80%	
EGFR IHC > 0	56%	1.00	82%	0.72
EGFR IHC = 0	56%		75%	
EGFR IHC ≥ 100	62%	0.31	79%	1.00
EGFR IHC < 100	48%		81%	
EGFR IHC ≥ 200	55%	1.00	77%	0.74
EGFR IHC < 200	56%		82%	
EGFR IHC = 300	56%	1.00	78%	1.00
EGFR IHC < 300	56%		81%	

PFS, progression-free survival; CI, confidence interval; OS, overall survival; FISH, Fluorescent in situ hybridization; IHC, immunohistochemistry; RR, response rate, DCR, disease control rate, EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma.

Table 4

Selected CAF Biomarkers

Analyte	N	PFS Hazard Ratio	95% Confidence Interval		*p*	OS Hazard Ratio	95% Confidence Interval		*p*
Hu HGF (62)	74	1.95	0.86	4.46	0.11	4.53	1.74	11.81	< 0.01
MMP-9 (27)	74	1.52	0.63	3.66	0.35	2.63	1.06	6.52	0.04
Osteopontin	71	1.63	0.71	3.75	0.25	3.15	1.24	8.04	0.02
Hu PDGF-bb (47)	74	0.37	0.15	0.90	0.03	0.58	0.23	1.46	0.25

Analyte	N	RR Odds Ratio [a]	95% Confidence Interval		p-value	DCR Odds Ratio [b]	95% Confidence Interval		p-value
Hu HGF (62)	69	1.34	0.24	7.46	0.74	14.82	1.33	164.69	0.03
Hu IL-18 (42)	69	2.99	0.53	16.97	0.22	29.72	2.25	392.94	0.01
MMP-9 (27)	69	3.14	0.51	19.35	0.22	11.62	1.01	133.07	0.049
Hu SCGF-b (78)	69	2.19	0.41	11.70	0.36	17.13	1.55	189.88	0.02
Hu VEGF (45)	69	1.55	0.22	11.12	0.66	22.30	1.60	311.24	0.02
sVEGFR2	68	0.28	0.05	1.59	0.15	0.01	<0.001	0.23	< 0.01

Relationship between baseline levels and OS and PFS.

[a] Odds of not achieving a response.

[b] Odds of not achieving stable disease or better.

CAF, cytokine-angiogenesis factor; PFS, progression-free survival; OS, overall survival; HGF, hepatocyte growth factor; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; RR, response rate; DCR, disease control rate; IL, interleukin; SCGF, stem cell growth factor; VEGF, vascular endothelial growth factor; sVEGFR, vascular endothelial growth factor receptor