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Paired Phase II Studies of Erlotinib/Bevacizumab in Advanced Bronchioloalveolar Carcinoma or in Never-Smokers with Advanced Non-Small-Cell Lung Cancer (NSCLC): SWOG S0635 and S0636 Trials

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Abstract

Background—Before mutation testing of the *epidermal growth factor receptor (EGFR)* gene was recognized as highly associated with activity of EGFR tyrosine kinase inhibitors (TKIs), clinically defined patient populations with bronchioloalveolar carcinoma (BAC) and never-smokers were identified as likely to benefit from EGFR TKIs. Based on preclinical and clinical data suggesting potentially improved efficacy with a combination of an EGFR TKI with the anti-angiogenic agent bevacizumab, SWOG initiated paired phase II trials to evaluate the combination of erlotinib/bevacizumab in patients with advanced BAC (S0635) or never-smokers with advanced lung adenocarcinoma (S0636).

Methods—Eligible patients with BAC or adeno/BAC (S0635) or never-smokers with advanced lung adenocarcinoma (S0636) received erlotinib 150 mg daily with bevacizumab 15 mg/kg until progression or prohibitive toxicity. Never-smokers with BAC were preferentially enrolled to S0636. The primary endpoint for both trials was overall survival (OS).

Results—A total of 84 patients were enrolled on S0635, 85 on S0636. The objective response rate was 22% (3% complete responses (CRs)) on S0635 and was 50% (38% confirmed; 3% CRs)

on S0636. Median progression-free survival was 5 and 7.4 months on S0635 and S0636, respectively. Median OS was 21 and 29.8 months, respectively. Toxicity consisted mainly of rash and diarrhea in both trials.

Conclusion—Though the field has moved toward molecular rather than clinical selection of patients as optimal candidates for EGFR TKI therapy, these results support the hypothesis that a subset of patients in whom erlotinib is particularly active may receive an incremental benefit from the addition of bevacizumab.

Background

Prior to the recognition that clinical efficacy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) was more highly associated with the presence of an activating *EGFR* mutation in tumor tissue than with clinical characteristics (1), clinical selection of patients likely to benefit from EGFR TKIs was a leading management strategy. Patients with the bronchioloalveolar carcinoma (BAC) subtype of non–small-cell lung cancer (NSCLC) and never-smokers were previously identified as being responsive (2) to these agents.

The clinico-pathologic entity of BAC has recently undergone redefinition as part of a new classification system for lung adenocarcinomas (3). This new classification revises the lepidic pattern of non-invasive, pure BAC as adenocarcinoma *in situ*, while the more prevalent adenocarcinoma with BAC features (adenoBAC) has been re-classified as either minimally invasive adenocarcinoma (for tumors ≤ 3 cm with a lepidic-predominant histologic pattern and an invasive component measuring ≤ 5mm) or lepidic-predominant invasive adenocarcinoma (for an invasive component > 5mm). Regardless of the histologic designation, this spectrum has been recognized as representing a subtype of NSCLC for which EGFR inhibitors have demonstrated particular efficacy, with a median overall survival (OS) of 13–17 months (2,4).

Never-smokers with advanced non-small cell lung cancer have also long been identified as a clinically distinct population. In addition to presenting at a younger median age, being disproportionately female, and demonstrating a histology of adenocarcinoma far more than other NSCLC subtypes (5,6), never-smokers were identified as the clinically defined subgroup most likely to benefit from epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Accordingly, this clinically defined subgroup became the subject of additional studies attempting to validate a clinical characteristic as a predictor of TKI (2,7) prior to the broad practice of molecular marker testing.

The combination of the oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib with the anti-angiogenic agent bevacizumab has been demonstrated to be feasible without unexpected toxicity, with a suggestion of improved efficacy in some patient subsets (8,9). SWOG S0635 (ClinicalTrials.gov Identifier: NCT00436332) and SWOG S0636 (ClinicalTrials.gov Identifier: NCT00445848) were paired multicenter phase II trials of the combination of erlotinib/bevacizumab, in patient populations with advanced BAC/adenoBAC or never-smokers with advanced lung adenocarcinoma, respectively, to

determine if a meaningful survival extension could be achieved that would warrant a randomized phase III trial.

METHODS

Eligibility

As defined by the 6th Edition of the AJCC staging system in place at the time this trial was initiated, patients were required to have histologically proven, stage IIIB (by pleural effusion) or IV lung adenocarcinoma. Enrollment to S0635 was limited to those with BAC or adenoBAC, as defined as a combination of lepidic predominant adenocarcinoma and invasive adenocarcinoma; this diagnosis could not be made by cytologic specimens, as these were considered insufficient for identifying the characteristic lepidic growth pattern of BAC/adenoBAC. Patients enrolled onto S0636 were required to be never smokers (<100 cigarettes over a lifetime).

For both studies, patients with a SWOG performance status (PS) of 0, 1, or 2 were eligible. All patients had evidence of measureable or non-measurable disease by computed tomography (CT) of the chest; to be included in the analysis of response patients were required to meet the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 definition of measurable disease (10).

No prior biologic therapy with an EGFR or angiogenesis inhibitor was allowed for either trial. There was no limit on number or duration of prior regimens of chemotherapy or other systemic treatments, which had to have been completed at least 4 weeks before enrollment on the present trial. Patients must have had adequate organ function as defined identically by the protocols.

Prior radiation was permitted in both S0635 and S0636 if at least 4 weeks had elapsed from radiation and disease was present outside of the radiation port. Though initially ineligible, patients with treated brain metastases or on a stable dose of anti-coagulation were permitted to enroll following amendment of the protocol.

All patients were informed of the investigational nature of the studies and signed a written informed consent in accordance with local institutional review board and federal guidelines.

Study Design

Treatment for both protocols consisted of erlotinib administered at a daily dose of 150 mg orally, with concurrent administration of bevacizumab at 15 mg/kg IV every 21 days; cycles were defined as 21 days. Delays in treatment and dose modification (for erlotinib only) were performed for grade 3/4 toxicity, for which treatment with either agent could be withheld for a maximum of 3 weeks. Treatment was restarted on improvement of toxicity to less than or equal to grade 1, or grade 2 with a dose reduction of erlotinib to 100 mg or 50 mg daily. Patients with significant bleeding events or sustained proteinuria did not restart bevacizumab but were permitted to remain on study receiving erlotinib alone.

Patients underwent repeat history and physical examination and laboratory assessment before each treatment period. Repeat CT imaging to assess response was performed following every two cycles initially, then gradually increased to longer intervals after six months without evidence of progression. Baseline CT imaging and the first two follow-up scans were requested to be performed with the same CT scanner and technique. Patients off treatment were observed at least every six months for two years and then annually until death or data cutoff. Patients were removed from protocol treatment for disease progression, unacceptable toxicity as assessed by the investigator, development of intercurrent, non-cancer related illnesses that prevented continuation of treatment, prolonged treatment delay, or based on patient request for any reason.

Study Evaluation and Statistical Methods

Toxicities were graded according to National Cancer Institute Common Toxicity Criteria Version 3.0. Response assessments (complete or partial response or stable disease) followed RECIST guidelines (10). Because the primary endpoint for both trials was OS, patients with only non-measurable disease were allowed to enroll. However, response assessments were not required for these patients.

The primary objective of both S0635 and S0636 was OS. Based on the results from prior studies of EGFR TKIs in advanced BAC and adenoBAC (2,4) and of a longer survival among never-smokers compared with others with advanced NSCLC who received EGFR TKIs (11), a prospective definition for both trials was established that this regimen would be of considerable interest if the true median OS exceeded 19 months, but would be of no further interest if the true median OS survival were less than 12 months. A target population of 80 patients for each trial accrued at a rate of 10 patients per month, with an additional 18 months of follow-up, would provide a power of 0.86 to rule out the null hypothesis of a 12 month median OS at a .05 level (indicating no further interest in the regimen) vs. an alternative of a 19 month median OS. It was prospectively defined that an observed median OS of 16 months or longer for both trials will be considered evidence that this regimen warrants further testing in a phase III setting, provided other factors such as toxicity appear favorable.

OS and PFS estimates were calculated using the method of Kaplan and Meier (12). Confidence intervals for the median overall and PFS were calculated according to the method of Brookmeyer and Crowley. (13) Response was assessed in the subset of patients with measurable disease at baseline. The response rate was defined as the total number of confirmed and unconfirmed complete and partial responders observed in this subset. The disease control rate was defined as the total number of patients with a best response of stable disease or better. Exact confidence intervals were calculated for binary outcomes.

For the S0635 data set, post-hoc landmark analysis was performed to look for differences in subsequent OS and PFS on the basis of development of acne/rash, diarrhea, or hypertension by day 42. Only patients alive at Day 42 were included in the analysis of OS, and only patients alive and progression-free at Day 42 were included in the analysis of PFS.

Submission of tissue was requested for all study participants on both trials for molecular marker studies. All analyses were performed at the University of Colorado. Studies for activating EGFR mutations used Sanger sequencing technology, which was routinely used at the time of this study start. Gene copy number for EGFR by fluorescence *in situ* hybridization (FISH) was studied according to methodology previously described (14). Markers for protein expression by immunohistochemistry (IHC) using H-score system (15) included: EGFR, E-cadherin, HER2 and Phospho-AKT (pAKT),

RESULTS

Patient Characteristics

S0635 and S0636 were activated together in July, 2007. S0636 enrolled more rapidly and was closed in September of 2010 with a total accrual of 89 patients, of whom two patients were ineligible due to incorrect histology; another two were not analyzable due to their not receiving any treatment on protocol. S0635 was closed with a total accrual of 84 patients in August of 2011, of whom two patients were ineligible, one due to incorrect histology, and another due to a history of cerebral aneurysm. Three additional patients are not evaluable due to never having received protocol-based therapy. The accrual rate of for S0635 of approximately two patients per month was below the historical accrual of SWOG on the preceding trial S0126 (16), likely because of the significant overlap of the trial eligibility with S0636, to which enrollment was prioritized.

Characteristics of the 79 assessable patients on S0635 and 85 on S0636 are presented in Table 1. For S0635, the median age was 69, with a range from 39 to 92 years of age. Thirty-eight patients (48%) were male and 41 (52%) were female. PS was 0 or 1 in 76 patients (96%). Stage IV disease was present in 76 patients (96%), while three patients (4%) had stage IIIB NSCLC with a pleural effusion. Measurable disease was present at baseline in 63 of 79 patients (80%).

For S0636, the median age was 61, with a range from 31 to 84 years of age. Fifty-six patients (66%) were female, and 29 (34%) were male. Racial background was Caucasian in 56 (66%), Asian in 21 (25%), 4 (5%) African American. PS was 0 or 1 in 82 patients (96%). Stage IV disease was present in 70 patients (82%), while 15 patients (18%) had stage IIIB NSCLC with a pleural effusion. Measurable disease was present at baseline in 66 of 85 patients (78%). Twenty-two patients (26%) had treated, asymptomatic brain metastases that were stable or improving at baseline. Eleven patients (13%) had received at least one prior systemic therapy for their disease.

Treatment Delivery

On S0635, the median number of cycles delivered was 7 (range 1–66). Of the 75 patients who have discontinued treatment at the time of this report, 9 (12%) were due to toxicity, each from a different issue ranging from severe rash to fatigue to non-healing skin ulcer to severe fatigue. Two patients (3%) discontinued protocol-based treatment due to patient preference. Based on calculation of medication delivered, 34 patients (43%) had a dose reduction of erlotinib. On S0636, the median number of cycles delivered was 10.5 (range 1–

55). 14 patients (16%) discontinued treatment due to toxicity, most commonly rash (3 patients), fatigue (3 patients), hypertension (2 patients), or diarrhea (2 patients). Four patients (5%) discontinued protocol-based treatment due to patient preference and in the absence of protocol-defined prohibitive toxicity. Based on calculation of medication delivered, 53 patients (62%) had a dose reduction or dose delay of erlotinib, while 26 patients (31%) had a dose delay of bevacizumab.

Time to Progression and Survival Analysis

With a median follow-up of 37.6 months among patients still alive from the S0635 trial, the median PFS was 5 (95% CI, 4 to 7) months (Figure 1, panel A). Median OS, illustrated by Kaplan-Meier plot in Figure 2, panel A, is 21 months (95% CI, 14 to 26 months), meeting the design-specified criterion of a median OS of 16 months or longer. Survival was 67% (95% CI: 56%–76%), 43% (95% CI: 32%–53%), and 34% (95% CI: 24%–45%) at one, two, and three years, respectively. Among 64 patients with follow-up data submitted, 43 have received additional therapy, with no further details available.

For S0636, with a median follow-up of 41.5 months among patients still alive, the median PFS was 7.4 (95% CI, 6.1 to 10.9) months (Figure 1, panel B). Median OS, illustrated by Kaplan-Meier plot in Figure 2, panel B, is 29.8 months (95% CI, 22.5 to 37.8 months), exceeding the design-specified criterion of a median OS of 16 months or longer. Survival was 78% (95% CI: 67%–85%), 57% (95% CI: 46%–67%), and 43% (95% CI: 32%–53%) at one, two, and three years, respectively. Sixty patients (71%) are known to have received additional therapy, with details not systematically collected.

Response

Best radiographic response among the 63 patients on S0635 and 66 on S0636 with measurable disease is shown in Table 2, with results also illustrated by waterfall plots in Figure 3, panels A (S0635) and B (S0636). On S0635, two patients (3%; 95% CI, 0% to 11%) achieved a confirmed complete response (CR), and twelve (19%; 95% CI, 10% to 31%) achieved a partial response (PR), 5 confirmed, 7 unconfirmed. Stable disease (SD) was observed as best response among 33 patients (52%), for a total disease control rate (CR+PR+SD) of 75% (95% CI: 62%–85%). Progressive disease (PD) was the best response in 10 patients (16%; 95% CI, 8% to 27%), while one additional patient (1%) experienced symptomatic deterioration felt consistent with PD. One patient died prior to any follow-up disease assessments (due to sudden cardiac arrest, unrelated to disease or protocol treatment) and three additional patients did not have reassessment adequate for determining response. All four patients (6%) are assumed to be nonresponders.

On S0636, two patients (3%; 95% CI, 0%–11%) achieved a confirmed complete response (CR), and 31 (47%; 95% CI, 35%–60%) achieved a partial response (PR), 23 confirmed, 8 unconfirmed. Stable disease (SD) was observed as best response among 23 patients (35%), for a total disease control rate (CR+PR+SD) of 85% (95% CI: 24%–48%). Progressive disease (PD) was the best response in 8 patients (12%; 95% CI, 5%–22%). Two additional patients (3%) did not have reassessment adequate for determining response and are counted in the denominator as non-responders.

Toxicity

Maximum toxicities of the combination of erlotinib with bevacizumab are illustrated in Table 3, which combine results for 161 patient receiving treatment on S0635 or S0636, as the treatment regimen and dose adjustments are shared between the two protocols. The most commonly reported adverse events were acne/rash (91% of patients, grade 3/4 in 13%), diarrhea (71% of patients, grade 3/4 in 10%), and fatigue (65%; grade 3/4 in 9%). A more complete list of common adverse events is listed in Table 3.

In addition, bleeding complications were observed in 39% of patients, which included epistaxis in 35% of patients (1% grade 3), CNS ischemia in 3 patients (2%, grade 3 or 4 in all), rectal bleeding in 11 patients (7%, none grade 3 or higher), and hemoptysis in 5 patients (3%, 1% grade 3), and a single patient (<1%) experiencing CNS hemorrhage (grade 1). Though a single patient on S0635 died of hypoxia that was listed as potentially attributable to treatment, this patient had very advanced disease at the start of treatment, with death far more likely due to disease progression.

Post-hoc subset analyses

Post-hoc landmark analyses were performed to look for differences in subsequent OS and PFS on the basis of development of acne/rash, diarrhea, or hypertension by day 42 in each of the trials. On S0635, patients who had developed diarrhea by Day 42 had better subsequent overall survival than those who had not ($p=0.01$, HR=0.50 (95% CI: 0.29–0.87)), though there was no significant difference in PFS, $p=0.37$. There were no significant differences in PFS or OS as a function of development of acne/rash or hypertension. No significant differences in PFS or OS emerged in association with toxicities in the S0636 protocol.

While tumor tissue was requested for molecular marker testing, only a very limited minority of patients ($N = 32$) on S0635 had tissue for *EGFR* molecular marker testing, of whom only 3 had an activating *EGFR* mutation identified. Of these, a patient with an L858R substitution and non-measurable disease died without demonstrated progression after 12.3 months, a patient with an exon 19 deletion achieved a CR but demonstrated progression after 7.4 months and died after 13.3 months, and an additional patient with an exon 19 deletion and non-measurable disease demonstrated a PFS of 30.1 months and died after 44.3 months. Overall, it was impossible to draw meaningful conclusions based on molecularly-defined subgroups.

Tissue was received from 66 patients on S0636. However, only 42 of those patients (64%) submitted specimens adequate for the testing performed in this protocol. Among 29 patients, who underwent EGFR FISH analysis, 14 pts (48%) were positive, including 9 pts (31%) with high polysomy and 5 pts (17%) with amplification. In the EGFR FISH+ group, the response rate was 57% versus 43% in the FISH- group, but no statistical significant associations to outcome (Table 4).

Among 29 patients, who underwent *EGFR* mutation analysis, 9 pts (31%) had EGFR mutant tumor and 20 pts (69%) *EGFR* wild type (wt) tumors. The patients with EGFR mutant tumors has a response rate of 89% versus 33% in the *EGFR* wt group, ($p=0.01$). However, there were no statistical significant associations with PFS or OS (Table 4).

IHC staining was done for both plasma and membrane, with results obtained from 44 patients. Using cytoplasm staining, 25 pts (57%) had a H-score of 0–200, and 19 pts (43%) had a H-score 201–400. An H-score > 200 was associated with better OS (HR=0.46, p=0.03) and PFS (HR=0.40, p=0.01) but not response (p=0.16). Results for membrane staining were similar.

We repeated the analyses of EGFR FISH and IHC excluding the 9 patients whose tumor had EGFR mutation. In these patients, an H-Score > 200 in cytoplasm was associated with OS (HR=0.40, p=0.04) and PFS, (HR=0.43, p=0.03) but not with response (p=0.37). An H-score > 200 in the membrane was associated with OS (HR=0.18, p=0.02), and PFS (HR=0.19, p=0.003) but not response (p=0.13). FISH positivity was not associated with OS (p=0.15), PFS (p=0.20), or response outcomes (p=1.00).

IHC was performed for E-cadherin and results were obtained from 48 patients. Comparing high expression (H score>200) versus low expression (H score ≤ 200), no statistically significant associations with response, PFS or OS for any of those biomarkers were observed. IHC was also performed for HER2 and pAKT. For HER2, H-score was 0–200 for 43/43 (100%), and for pAKT H-Score was 0–200 for 45/47(96%).

It is important to note that all of the analyses describe above were exploratory with no adjustment for multiple comparisons. Any of the associations noted with a p-value less than 0.05 will need to be validated in future studies.

Given the absence of any reliable marker correlated with anti-angiogenic therapy in prior studies, no evaluations of potential molecular markers relevant to angiogenic activity were pursued.

DISCUSSION

Over the conduct of these studies, data emerged from the IPASS trial (1) that provided compelling evidence of the superiority of molecular selection as a function of *EGFR* activating gene compared with other molecular markers as well as histologic features such as BAC histology or clinical variables such as smoking status. On the basis of this work, EGFR TKI therapy is recommended as first line therapy on the basis of *EGFR* mutation but not based on BAC histology or a patient being a never-smoker (17). Nevertheless, the high proportion of *EGFR* mutations in these clinically defined subsets is consistent with these variables still enriching for a high probability of benefit from EGFR TKI therapy (2). Recent results from a prospectively defined population of 152 Japanese patients with an activating *EGFR* mutation in exon 19 or 21 that randomized EGFR TKI-naïve patients to receive erlotinib with or without bevacizumab has shown a significantly higher median PFS, 16.0 vs. 9.7 months, with the combination, with OS not yet reported (18). Additional supportive data come from the single arm European BELIEF trial of erlotinib with bevacizumab, which demonstrated efficacy far exceeding expected results for erlotinib monotherapy (19). On the basis of these data, this combination has recently been approved by the European Commission for European Union patients in Europe with advanced NSCLC that harbors an activating *EGFR* mutation (20). In addition, a North American randomized phase II trial of

erlotinib vs. erlotinib/bevacizumab in *EGFR* mutation-positive NSCLC being conducted by Academic and Community Cancer Research United (ACCRU) is also addressing the incremental benefit of bevacizumab with erlotinib in this setting and has recently completed enrollment (21).

The management and even existence of a distinct clinical entity of BAC has been the subject of significant changes since the inception and conduct of SWOG 0635. While still sometimes considered a distinct category of NSCLC among clinical oncologists, the new categorization of lung adenocarcinomas (3) redefines multifocal BAC as lepidic predominant adenocarcinoma. Though BAC and adeno/BAC were the descriptors employed for this study to describe lepidic predominant lung adenocarcinoma or mucinous adenocarcinoma without or with an invasive component, respectively, this classification has now been obviated. Because we relied on an institutional definition for eligibility, we are unable to classify subsets of patients as having what was previously characterized as non-mucinous or mucinous BAC, since this was inconsistently reported

Along with the fundamental redefinition of NSCLC that removes the BAC subgroup, the management of NSCLC has evolved over the years since both of these trials were developed, now following an algorithm defined by the presence or absence of a driver mutation such as an *EGFR* gene mutation or several others. Like patients with a histology formerly identified as BAC or adeno/BAC, never-smokers follow a treatment path based on the presence of an activating *EGFR* mutation or other biomarker.

There was no evidence of a significant difference in outcomes as the presence or absence of rash, or hypertension, though development of diarrhea was associated with a significantly longer OS. In the absence of a significant improvement in PFS, this observation is provocative but difficult to interpret without this question being addressed in other data sets with *EGFR* TKIs. The favorable tolerability of this combination in both trial populations was also notable.

Molecular marker testing was only very limited in S0635, so it is unknown whether markedly greater efficacy was limited to specific molecularly-defined subgroups. Unfortunately, our efforts to perform molecular characterization of patient tumors on S0635 was profoundly limited by only having sufficient tissue submitted to perform any testing for 32 patients. In addition to this yielding too little information on *EGFR* mutation status to draw meaningful conclusions, we did not test for *KRAS* mutations, another potentially relevant molecular marker reported as common in the subset of NSCLC tumors previously defined as the mucinous subtype of BAC (15), associated with a very low probability of significant benefit from *EGFR* TKI-directed therapies (16).

The molecular marker correlates from S0636 revealed that patients with tumors demonstrating high *EGFR* protein expression had a superior OS and PFS compared to the patients with tumors having no or low *EGFR* protein expression, though only the association with PFS was statistically significant. Due to the small number of patients, we must interpret these results with caution, and a prognostic association cannot be ruled out. Notably, in

larger studies with EGFR TKIs in NSCLC, the protein expression has not shown to be of significant predictive value (22).

Despite these limitations, the results from the S0635 and S0636 studies, taken together, corroborate the conclusion that a subset of patients benefit from addition of bevacizumab to erlotinib. The S0635 trial demonstrated a median OS of 21 months, surpassing the prospectively defined threshold median OS of 19 months as well as the median OS of 13 months with gefitinib (16) and 17 months with erlotinib (2) in this clinically defined population. Molecular marker testing was only very limited in this multicenter trial, so it is unknown whether markedly greater efficacy was limited to specific molecularly-defined subgroups. Similarly, though S0636 did not employ molecular selection and is known to include many patients without an *EGFR* mutation, the median OS of 29 months far exceeds our prospectively identified threshold for considerable interest of 19 months and is remarkable for a population that is not comprised exclusively of molecularly selected patients. We look forward to the results of randomized trials evaluating this combination versus monotherapy in broader patient populations with EGFR mutated tumors.

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Figure 1.
Progression-Free Survival
Kaplan-Meier curves for progression-free survival on S0635 (panel A) and S0636 (panel B)

Figure 2.
Overall Survival
Kaplan-Meier curves for overall survival on S0635 (panel A) and S0636 (panel B)

Figure 3.
Waterfall plots for measurable response
Waterfall plots for objective tumor response on S0635 (panel A) and S0636 (panel B)

Table 1

Demographics of eligible patients on SWOG S0635 and S0636.

	<u>Patients enrolled</u> <u>N = 79</u>	<u>Patients enrolled</u> <u>N = 85</u>
Median Age (range)	69 (39 – 92)	61 (31 – 84)
Sex		
Male	38 (48%)	29 (34%)
Female	41 (52%)	56 (66%)
Race		
Caucasian	72 (91%)	56 (66%)
African American	6 (8%)	4 (5%)
Asian	0 (0%)	21 (25%)
Native American	0 (0%)	2 (2%)
Unknown	1 (1%)	2 (2%)
Performance Status		
0/1	76 (96%)	82 (96%)
2	3 (4%)	3 (4%)
Pathology		
AdenoBAC	56 (71%)	n/a
BAC	23 (29%)	
Stage		
IIIB (pleural effusion)	3 (4%)	15 (18%)
IV	94 (94%)	70 (82%)
Smoking History		
Current	11 (14%)	n/a
Former	61 (77%)	
Never	7 (9%)	

Table 2

Best response in evaluable patients on SWOG S0635 and S0636.

Response	S0635 evaluable patients (N = 63)	S0636 evaluable patients (N = 66)
Complete Response (CR)	2 (3%)	2 (3%)
Partial Response (PR)	12 (19%)	31 (47%)
Objective Response Rate (CR+PR)	14(22%)	33 (50%)
Stable Disease (SD)	33 (52%)	23 (35%)
Non-Progression (ORR + SD)	47 (75%)	56 (85%)
Progressive Disease (PD)	11 (17%)	8 (12%)
Symptomatic Deterioration	1 (2%)	0 (0%)
Not Determinable *	4 (6%)	2 (3%)

* Early death or inadequate assessment

Table 3

Most common adverse events (>15% of patients) and bleeding complications on the combination of daily oral erlotinib with intravenous bevacizumab every 21 days, combined results from SWOG S0635 and SWOG 0636.

Toxicity	% Overall [Grade 1] (% Grade 3/4) (N = 161)
Any adverse event	98 (52)
Acne/Rash	91 (13)
Diarrhea	71 (10)
Fatigue	65 (9)
Nausea	41 (2)
Mucositis	35 (2)
Hypertension	34 (13)
Weight loss	32 (3)
Anorexia	32 (2)
Elevated transaminases	31 (4)
Dry Skin	27 (1)
Alopecia	27 (0)
Musculoskeletal pain	26 (2)
Cough	24 (0)
Taste alteration	22 (0)
Proteinuria	21 (5)
Elevated bilirubin	21 (1)
Elevated creatinine	19 (1)
Voice changes	19 (1)
Headache	18 (1)
Hypoalbuminemia	18 (1)
Vomiting	18 (1)
Decreased hemoglobin	18 (1)
Dyspnea	17 (1)
Hyponatremia	15 (4)
Bleeding Complications	42 (2)
Epistaxis	35 (1)
Rectal bleeding	7 (0)
Hemoptysis	3 (1)

Table 4

Key molecular marker results EGFR mutation, FISH, and IHC on the subset of patients with sufficient tissue available, correlated with efficacy endpoints on SWOG S0636.

	N		HR (OS)	HR (PFS)
EGFR FISH			0.56	0.66
Positive	14	(8/14) 57%	(0.26–1.20)	(0.33–1.30)
Negative	14	(6/14) 43%	p=0.13	P=0.23
		p=0.71		
EGFR Mut			1.12	0.71
Wt	20	(6/18) 33%	(0.50–2.54)	(0.33–1.51)
Mut	9	(8/9) 89%	p=0.78	p=0.37
		p=0.01		
EGFR IHC (cytoplasm)			0.46 (0.23–0.93)	0.40 (0.21–0.79)
0–200	25	(6/17) 35%	P=0.03	(p=0.01)
>200	19	(9/14) 64%		
		P=0.16		
EGFR IHC (membrane)			0.35 (0.15–0.86)	0.24 (0.10–0.55)
0–200	32	(7/20) 35%	P=0.02	(p=0.001)
>200	12	(8/11) 73%		
		P=0.07		
ECAD IHC			1.13	1.08
0–200	14	(5/10) 50%	(0.55–2.32)	(0.56–2.07)
>200	34	(12/26) 46%	P=0.74	(p=0.82)
		P=1.00		