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Authors

West, Howard L

Moon, James

Wozniak, Antoinette J

et al.

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Paired Phase II Studies of Erlotinib/Bevacizumab for Advanced Bronchioloalveolar Carcinoma or Never Smokers With Advanced Non–Small-cell Lung Cancer: SWOG S0635 and S0636 Trials

Howard L. West,¹ James Moon,² Antoinette J. Wozniak,³ Philip Mack,⁴ Fred R. Hirsch,⁵ Martin J. Bury,⁶ Myron Kwong,⁷ Dorothy D. Nguyen,⁸ Dennis F. Moore,⁹ Jieling Miao,² Mary Redman,² Karen Kelly,⁴ David R. Gandara⁴

Abstract

Paired phase II trials, Southwestern Oncology Group S0635 and S0636, administered erlotinib/bevacizumab to 84 patients with advanced bronchioloalveolar carcinoma or 85 never smokers with advanced lung adenocarcinoma, respectively. Efficacy, in particular, the primary endpoint of overall survival, well exceeded previous benchmarks, and the combination demonstrated no unexpected toxicity challenges. These results suggest that the erlotinib/bevacizumab combination might confer a clinical benefit for selected patients.

Background: Before mutation testing of the epidermal growth factor receptor (*EGFR*) gene was recognized as highly associated with the 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. From preclinical and clinical data suggesting potentially improved efficacy with a combination of an EGFR TKI and the antiangiogenic agent bevacizumab, the Southwestern Oncology Group (SWOG) initiated paired phase II trials to evaluate the combination of erlotinib/bevacizumab in patients with advanced BAC (SWOG S0635) or never smokers with advanced lung adenocarcinoma (SWOG S0636). **Materials and Methods:** Eligible patients with BAC or adenocarcinoma with BAC features (SWOG S0635) or never smokers with advanced lung adenocarcinoma (SWOG S0636) received erlotinib 150 mg/day with bevacizumab 15 mg/kg until progression or prohibitive toxicity. Never smokers with BAC were preferentially enrolled to SWOG S0636. The primary endpoint for both trials was overall survival. **Results:** A total of 84 patients were enrolled in the SWOG S0635 trial and 85 in the SWOG S0636 trial. The objective response rate was 22% (3% complete response) in the SWOG S0635 trial and 50% (38% confirmed; 3% complete response) in the SWOG S0636 trial. The median progression-free survival was 5 and 7.4 months in the S0635 and S0636 trials, respectively. The median overall survival was 21 and 29.8 months, respectively. Toxicity consisted mainly of rash and diarrhea in both trials. **Conclusion:** Although 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 could receive an incremental benefit from the addition of bevacizumab.

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Keywords: Antiangiogenesis, BAC, Bronchioloalveolar, EGFR, Lepidic, Never-smoker

¹Swedish Cancer Institute, Seattle, WA

²Southwestern Oncology Group Statistical Center, Seattle, WA

³Karmanos Cancer Institute, Wayne State University, Detroit, MI

⁴Department of Medical Oncology, University of California, Davis, Cancer Center, Sacramento, CA

⁵Department of Medical Oncology, University of Colorado Cancer Center, University of Colorado, Aurora, CO

⁶Grand Rapids Community Clinical Oncology Program, Grand Rapids, MI

⁷Kaiser Permanente Medical Center, San Jose, CA

⁸Kaiser Permanente Medical Center, Redwood City, CA

⁹Cancer Center of Kansas, Wichita Community Clinical Oncology Program, Wichita, KS

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Address for correspondence: Howard L. West, MD, Swedish Cancer Institute, 1221 Madison Street, Suite 200, Seattle, WA 98104

E-mail contact: howard.west@swedish.org

Paired Phase II Studies of Erlotinib/Bevacizumab for BAC and NSCLC

Introduction

Before the recognition that the 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 the 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 to these agents.²

The clinicopathologic entity of BAC has recently undergone redefinition as a part of a new classification system for lung adenocarcinoma.³ This new classification has revised the lepidic pattern of noninvasive, pure BAC as adenocarcinoma in situ. Also, the more prevalent adenocarcinoma with BAC features (adenoBAC) has been reclassified as either minimally invasive adenocarcinoma (for tumors ≤ 3 cm with a lepidic-predominant histologic pattern and an invasive component measuring ≤ 5 mm) or lepidic-predominant invasive adenocarcinoma (for tumors with an invasive component > 5 mm). 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 to 17 months.^{2,4}

Never smokers with advanced NSCLC have also long been identified as a clinically distinct population. In addition to presenting at a younger median age, being disproportionately female, and demonstrating histologic features of adenocarcinoma far more than other NSCLC subtypes,^{5,6} never smokers were identified as a clinically defined subgroup most likely to benefit from EGFR TKIs. Accordingly, this clinically defined subgroup became the subject of additional studies attempting to validate a clinical characteristic as a predictor of TKI efficacy^{2,7} before the broad practice of molecular marker testing.

The combination of the oral EGFR TKI erlotinib with the antiangiogenic agent bevacizumab has been demonstrated to be feasible without unexpected toxicity, with a suggestion of improved efficacy in some patient subsets.^{8,9} The Southwestern Oncology Group (SWOG) S0635 trial (ClinicalTrials.gov identifier, NCT00436332) and SWOG S0636 trial (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 whether a meaningful survival extension could be achieved that would warrant a randomized phase III trial.

Materials and Methods

Eligibility

As defined by the sixth edition of the American Joint Committee on Cancer staging system in place when the trial was initiated, the patients were required to have histologically proven, stage IIIB (by pleural effusion) or IV lung adenocarcinoma. Enrollment to SWOG S0635 was limited to those with BAC or adenoBAC, defined as a combination of lepidic predominant adenocarcinoma and invasive adenocarcinoma. This diagnosis could not have been made by cytologic specimens, because these were considered insufficient for identifying the characteristic lepidic growth pattern of BAC/

adenoBAC. Patients enrolled in the SWOG S0636 trial were required to be never smokers (< 100 cigarettes in a lifetime).

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

No previous biologic therapy with an EGFR or angiogenesis inhibitor was allowed for either trial. No limit was given regarding the number or duration of previous regimens of chemotherapy or other systemic treatments. However, these had to have been completed ≥ 4 weeks before enrollment in the present trial. Also, the patients were required to have adequate organ function, as defined identically by the protocols.

Previous radiation was permitted in both S0635 and S0636 if ≥ 4 weeks had elapsed from radiation and disease was present outside the radiation port. Although initially ineligible, patients with treated brain metastases or receiving a stable dose of anticoagulation were permitted to enroll after amendment of the protocols.

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

Study Design

The 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 intravenously every 21 days. The cycles were defined as 21 days. Delays in treatment and dose modification (for erlotinib only) occurred for grade 3/4 toxicity, for which treatment with either agent could be withheld for a maximum of 3 weeks. Treatment was restarted with improvement of toxicity 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 continue in the study receiving erlotinib alone.

Patients underwent repeat history and physical examination and laboratory assessment before each treatment cycle. Repeat CT to assess for response was performed after every 2 cycles initially and gradually increased to longer intervals after 6 months without evidence of progression. Baseline CT imaging and the first 2 follow-up scans were required to be performed using the same CT scanner and technique. Patients not receiving treatment were observed at least every 6 months for 2 years and then annually until death or data cutoff. Patients were removed from the protocol treatment because of disease progression, unacceptable toxicity as assessed by the investigator, the development of intercurrent, non–cancer-related illnesses that prevented continuation of treatment, a prolonged treatment delay, or by patient request for any reason.

Study Evaluation and Statistical Analysis

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Response assessments (complete or partial response or stable disease) followed the Response Evaluation Criteria In Solid Tumors guidelines.¹⁰ Because the primary endpoint for both trials was OS,

Table 1 Demographic Data of Eligible Patients in SWOG S0635 and S0636 Trials

Variable	SWOG S0635 (n = 79)	SWOG S0636 (n = 85)
Age (y)		
Median	69	61
Range	39-92	31-84
Sex		
Male	38 (48)	29 (34)
Female	41 (52)	56 (66)
Race		
White	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)
Pathologic type		NA
AdenoBAC	56 (71)	
BAC	23 (29)	
Stage		
IIIB (pleural effusion)	3 (4)	15 (18)
IV	94 (94)	70 (82)
Smoking history		NA
Current	11 (14)	
Former	61 (77)	
Never	7 (9)	

Data presented as n (%).
Abbreviations: AdenoBAC = adenocarcinoma with bronchioloalveolar carcinoma features; BAC = bronchioloalveolar carcinoma; NA = not applicable; SWOG = Southwestern Oncology Group.

patients with only nonmeasurable disease were also allowed to enroll. However, response assessments were not required for these patients.

The primary objective of both trials (SWOG S0635 and S0636) was OS. Based on the results from previous studies of EGFR TKIs for advanced BAC and adenoBAC^{2,4} and the 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 the regimen would be of considerable interest if the true median OS was > 19 months. However, it was determined that the regimen would be of no further interest if the true median OS was < 12 months. A target population of 80 patients for each trial accrued at a rate of 10 patients monthly, 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 significance level (indicating no further interest in the regimen) versus the alternative 19-month median OS. It was prospectively defined that an observed median OS of \geq 16 months for both trials would be considered evidence that the regimen warranted further testing in a phase III setting, provided other factors, such as toxicity, appeared favorable.

The OS and progression-free survival (PFS) estimates were calculated using the Kaplan-Meier method.¹² The 95% confidence intervals (CIs) for median OS and PFS were calculated using 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 responses 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 95% CIs were calculated for the binary outcomes.

For the SWOG S0635 data set, a post hoc landmark analysis was performed to find differences in subsequent OS and PFS on the basis of the development of acne or 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 without progression at day 42 were included in the analysis of PFS.

The submission of tissue was requested for all study participants in both trials for the molecular marker studies. All analyses were performed at the University of Colorado. The studies to find activating EGFR mutations used Sanger sequencing technology, which was in routine use at the start of the trial. The gene copy number for EGFR by fluorescence in situ hybridization (FISH) was studied according to a previously described method.¹⁴ The markers for protein expression by immunohistochemistry (IHC) using the H-score system¹⁵ included EGFR, E-cadherin, HER2, and phospho-AKT (pAKT).

Results

Patient Characteristics

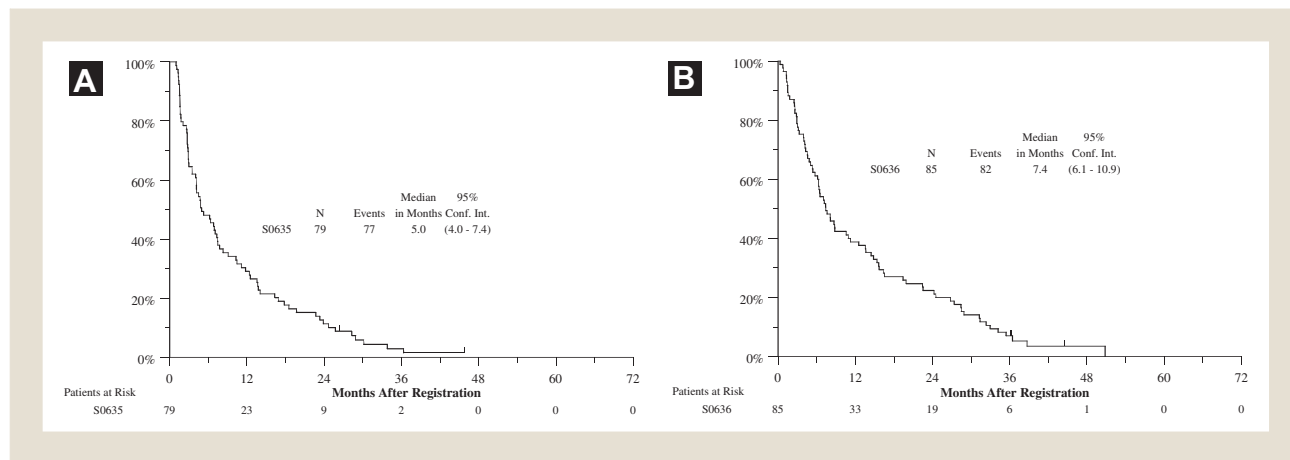
The SWOG S0635 and S0636 trials were activated together in July 2007. Patients were enrolled more rapidly in the SWOG S0636 trial, which was closed in September 2010, with a total accrual of 89 patients. Of these 89 patients, 2 were ineligible owing to incorrect histologic features and the data from 2 were not analyzable because they had not received any protocol-based treatment. The SWOG S0635 trial was closed in August 2011 with a total accrual of 84 patients. Of these 84 patients, 2 were ineligible, 1 because incorrect histologic features and 1 because of a history of cerebral aneurysm. The data from 3 additional patients were not evaluable because the patients had never received protocol-based therapy. The accrual rate for the SWOG S0635 trial of approximately 2 patients monthly was less than the historical accrual of SWOG in the preceding S0126 trial,¹⁶ likely because of the significant overlap in trial eligibility with S0636, to which enrollment was prioritized.

The characteristics of the 79 assessable patients in the SWOG S0635 trial and 85 in the SWOG S0636 trial are listed in Table 1. For S0635, the median patient age was 69 years (range, 39-92), and 38 patients (48%) were male and 41 (52%) were female. The PS was 0 or 1 in 76 patients (96%). Stage IV disease was present in 76 patients (96%), and 3 patients (4%) had stage IIIB NSCLC with pleural effusion. Measurable disease was present at baseline in 63 of the 79 patients (80%).

For S0636, the median patient age was 61 years (range, 31-84 years); 56 (66%) were female and 29 (34%) were male. The racial background was white in 56 (66%), Asian in 21 (25%), and African American in 4 (5%). The PS was 0 or 1 in 82 patients (96%). Stage

Paired Phase II Studies of Erlotinib/Bevacizumab for BAC and NSCLC

Figure 1 Kaplan-Meier Curves for Progression-free Survival in Southwestern Oncology Group (A) S0635 Trial and (B) S0636 Trial



IV disease was present in 70 patients (82%), and 15 patients (18%) had stage IIIB NSCLC with 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 ≥ 1 previous systemic therapy for their disease.

Treatment Delivery

In the SWOG S0635 trial, the median number of cycles delivered was 7 (range, 1-66). Of the 75 patients who had discontinued treatment at the writing of this report, 9 (12%) discontinued because of toxicity, each for a different issue ranging from severe rash to fatigue to a nonhealing skin ulcer to severe fatigue. Two patients (3%) discontinued protocol-based treatment by patient preference. According to the calculation of medication delivered, 34 patients (43%) had a dose reduction of erlotinib. In the SWOG S0636 trial, the median number of cycles delivered was 10.5 (range, 1-55). Fourteen patients (16%) discontinued treatment because of toxicity, most commonly rash (3 patients), fatigue (3 patients),

hypertension (2 patients), or diarrhea (2 patients). Four patients (5%) discontinued protocol-based treatment by patient preference, in the absence of protocol-defined prohibitive toxicity. According to the calculation of medication delivered, 53 patients (62%) had a dose reduction or dose delay of erlotinib, and 26 patients (31%) had a dose delay of bevacizumab.

Interval to Progression and Survival Analysis

With a median follow-up period of 37.6 months for patients still alive in the S0635 trial, the median PFS was 5 months (95% CI, 4-7 months; Figure 1A). The median OS, illustrated by the Kaplan-Meier plot in Figure 2A, was 21 months (95% CI, 14-26 months), meeting the design-specified criterion of a median OS of ≥ 16 months. The survival rate was 67% (95% CI, 56%-76%), 43% (95% CI, 32%-53%), and 34% (95% CI, 24%-45%) at 1, 2, and 3 years, respectively. Of the 64 patients with follow-up data submitted, 43 had received additional therapy, with no further details available.

For S0636, with a median follow-up period of 41.5 months for patients still alive, the median PFS was 7.4 months (95% CI, 6.1-10.9

Figure 2 Kaplan-Meier Curves for Overall Survival in Southwestern Oncology Group (A) S0635 Trial and (B) S0636 Trial

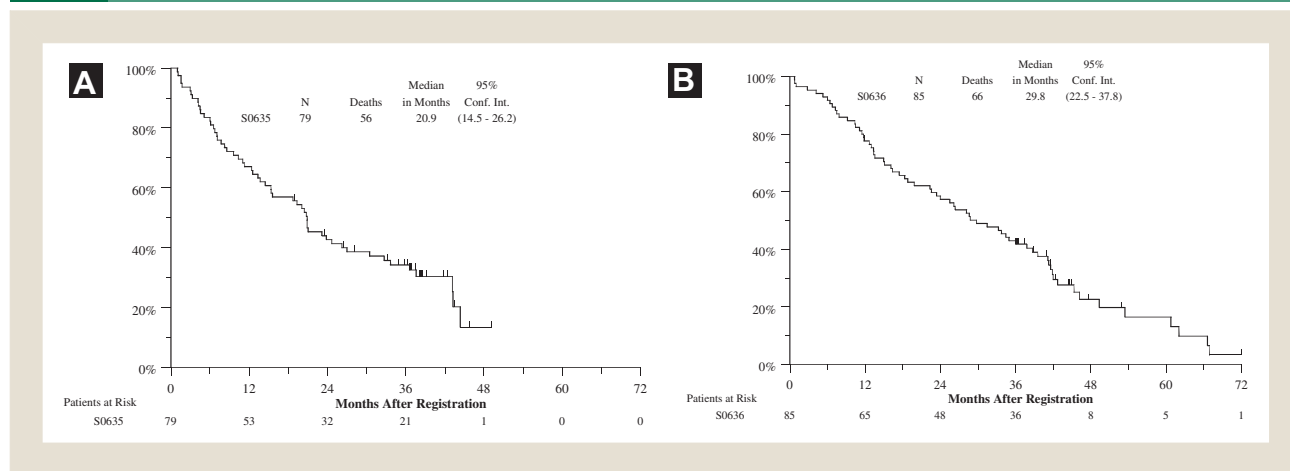


Table 2 Best Response in Evaluable Patients in SWOG S0635 and S0636 Trials

Response	SWOG S0635 Evaluable Patients (n = 63)	SWOG S0636 Evaluable Patients (n = 66)
CR	2 (3)	2 (3)
PR	12 (19)	31 (47)
OR (CR + PR)	14 (22)	33 (50)
SD	33 (52)	23 (35)
No progression (OR + SD)	47 (75)	56 (85)
PD	11 (17)	8 (12)
Symptomatic deterioration	1 (2)	0 (0)
Not determinable ^a	4 (6)	2 (3)

Data presented as n (%).

Abbreviations: CR = complete response; OR = overall response; PD = progressive disease; PR = partial response; SD = stable disease; SWOG = Southwestern Oncology Group.

^aEarly death or inadequate assessment.

months; Figure 1B). The median OS, illustrated by the Kaplan-Meier plot in Figure 2B, was 29.8 months (95% CI, 22.5-37.8 months), exceeding the design-specified criterion of a median OS of ≥ 16 months. The survival rate was 78% (95% CI, 67%-85%), 57% (95% CI, 46%-67%), and 43% (95% CI, 32%-53%) at 1, 2, and 3 years, respectively. Of the 85 patients, 60 (71%) were known to have received additional therapy, with the details not systematically collected.

Response

The best radiographic response among the 63 patients in the S0635 and 66 patients in the S0636 trials with measurable disease is listed in Table 2. The results are also illustrated by waterfall plots in Figure 3. In the SWOG S0635 trial, 2 patients (3%; 95% CI, 0%-11%) achieved a confirmed complete response (CR) and 12 (19%; 95% CI, 10%-31%) achieved a partial response (PR; 5 confirmed and 7 unconfirmed). Stable disease (SD) was observed as the best response in 33 patients (52%), for a total disease control rate (CR +

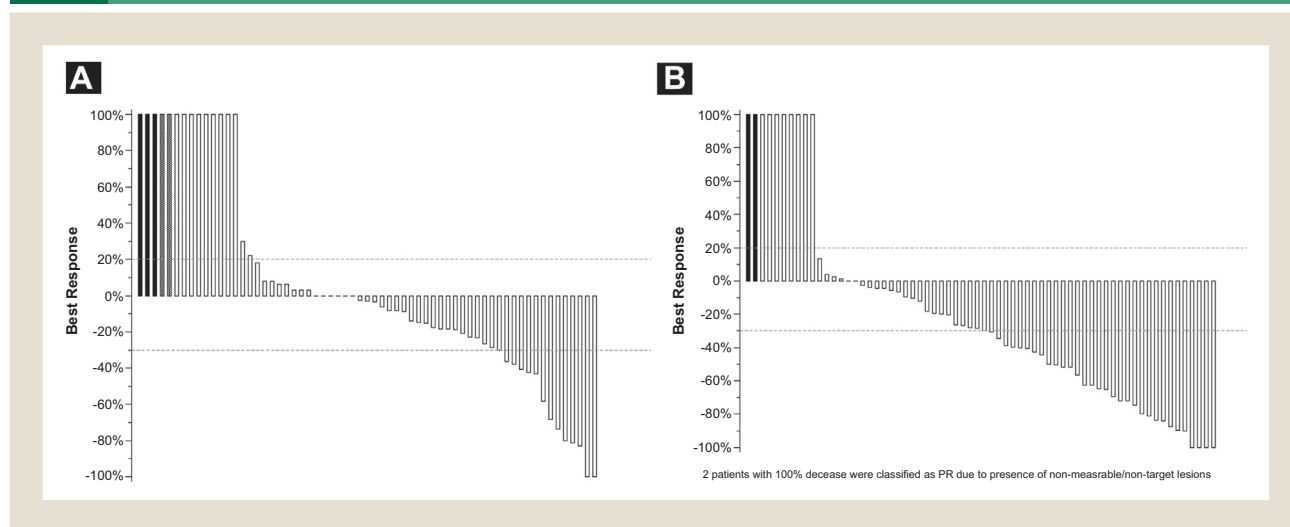
PR + SD) of 75% (95% CI, 62%-85%). Progressive disease (PD) was the best response in 10 patients (16%; 95% CI, 8%-27%), and 1 additional patient (1%) experienced symptomatic deterioration thought to be consistent with PD. One patient died (of sudden cardiac arrest, unrelated to disease or protocol treatment) before any follow-up disease assessments were performed, and 3 additional patients did not have reassessment data adequate for determining the response. All 4 patients (6%) were assumed to have no response.

In the SWOG S0636 trial, 2 patients (3%; 95% CI, 0%-11%) achieved a confirmed CR, and 31 (47%; 95% CI, 35%-60%) achieved a PR (23 confirmed and 8 unconfirmed). SD was observed as the best response in 23 patients (35%), for a total disease control rate (CR + PR + SD) of 85% (95% CI, 74%-94%). PD was the best response in 8 patients (12%; 95% CI, 5%-22%). Two additional patients (3%) did not have reassessment data adequate for determining the response and were counted in the denominator as nonresponders.

Toxicity

The maximum toxicities of the combination of erlotinib with bevacizumab are listed in Table 3, with the results combined for the 161 patients receiving treatment in the 2 trials, because the treatment regimen and dose adjustments were shared between the 2 protocols. The most commonly reported adverse events were acne or 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 given in Table 3.

In addition, bleeding complications were observed in 39% of patients, which included epistaxis in 35% of patients (1% with grade 3), central nervous system ischemia in 3 patients (2%; grade 3 or 4 in all), rectal bleeding in 11 patients (7%; none with grade ≥ 3), and hemoptysis in 5 patients (3%; 1% with grade 3), and central nervous system hemorrhage in 1 patient (< 1%; grade 1). Although a single patient in the S0635 trial died of hypoxia, considered potentially attributable to treatment, the patient had had very advanced disease at the start of treatment, with death far more likely from disease progression.

Figure 3 Waterfall Plots for Objective Tumor Response in Southwestern Oncology Group (A) S0635 Trial and (B) S0636 Trial

Paired Phase II Studies of Erlotinib/Bevacizumab for BAC and NSCLC

Table 3 Most Common Adverse Events (> 15% of Patients) and Bleeding Complications: Combined Results From SWOG S0635 and SWOG 0636 Trials (n = 161)

Toxicity	Overall (ie, Grade ≥ 1) ^a
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)

Abbreviation: SWOG = Southwestern Oncology Group.

^aData presented as percentages; data in parentheses are percentages of grade 3/4 toxicity.

Post Hoc Subset Analyses

Post hoc landmark analyses were performed to find any differences in subsequent OS and PFS on the basis of the development of acne or rash, diarrhea, or hypertension by day 42 in each of the trials. In the S0635 trial, patients who had developed diarrhea by day 42 had better subsequent OS than those who had not (hazard ratio [HR], 0.50; 95% CI, 0.29-0.87), although no significant difference was found in PFS ($P = .37$). No significant differences were found in PFS or OS as a function of the development of acne/rash or hypertension. No significant differences in PFS or OS emerged in association with toxicity in the S0636 protocol.

Although tumor tissue was requested for molecular marker testing, only a very limited number of patients (n = 32) in the S0635 trial had tissue available for *EGFR* molecular marker testing. Of these 32 patients, only 3 had an activating *EGFR* mutation identified. Of these 3 patients, 1 patient with an L858R substitution and nonmeasurable disease died without PD demonstrated after

12.3 months, 1 patient with an exon 19 deletion achieved a CR but demonstrated PD after 7.4 months and died after 13.3 months, and 1 patient with an exon 19 deletion and nonmeasurable disease had PFS of 30.1 months and died after 44.3 months. Overall, it was impossible to draw meaningful conclusions from the molecularly defined subgroups.

Tissue was received from 66 patients in the S0636 trial. However, only 42 of those patients (64%) had specimens adequate for the testing performed in this protocol. Of the 29 patients who had undergone *EGFR* FISH analysis, 14 (48%) had positive results, including 9 (31%) with high polysomy and 5 (17%) with amplification. In the *EGFR* FISH⁺ group, the response rate was 57% compared with 43% in the FISH⁻ group; however, no statistically significant associations with outcome were found (Table 4).

Of the 29 patients who underwent *EGFR* mutation analysis, 9 (31%) had an *EGFR*-mutant tumor and 20 (69%) had *EGFR* wild-type tumors. The patients with *EGFR*-mutant tumors had a response rate of 89% versus 33% in the *EGFR* wild-type group ($P = .01$). However, no statistically significant associations were found with PFS or OS (Table 4).

IHC staining was performed for both plasma and membrane, with results obtained for 44 patients. Using cytoplasm staining, 25 patients (57%) had an H-score of 0 to 200 and 19 patients (43%) an H-score of 201 to 400. An H-score > 200 was associated with better OS (HR, 0.46; $P = .03$) and PFS (HR, 0.40; $P = .01$) but not response ($P = .16$). The results for membrane staining were similar.

We repeated the analyses of *EGFR* FISH and IHC, excluding the 9 patients whose tumor had an *EGFR* mutation. In these patients, an H-score > 200 in the cytoplasm was associated with OS (HR, 0.40; $P = .04$) and PFS (HR, 0.43; $P = .03$) but not with response ($P = .37$). An H-score > 200 in the membrane was associated with OS (HR, 0.18; $P = .02$) and PFS (HR, 0.19; $P = .003$) but not with response ($P = .13$). FISH positivity was not associated with OS ($P = .15$), PFS ($P = .20$), or response outcomes ($P = 1.00$).

IHC was performed for E-cadherin, and results were obtained for 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, the H-score was 0 to 200 for 43 patients (100%), and for pAKT, the H-score was 0 to 200 for 45 of 47 patients (96%).

All the analyses were exploratory with no adjustment for multiple comparisons. Any of the associations noted with $P < .05$ require validation in future studies.

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

Discussion

During the conduct of these studies, data emerged from the IPASS (first line IRESSA vs. carboplatin/paclitaxel in Asia) trial¹ that provided compelling evidence of the superiority of molecular selection as a function of the *EGFR* activating gene compared with other molecular markers and histologic features such as BAC histologic features or clinical variables such as smoking status. On the basis of that trial, *EGFR* TKI therapy has been recommended as

Table 4 Key Molecular Marker Results for EGFR Mutation, FISH, and IHC for Subset of Patients With Sufficient Tissue Available, Correlated With Efficacy Endpoints in SWOG S0636

Variable	Patients (n)	Response Rate	HR (95% CI)	
			OS	PFS
EGFR FISH			0.56 (0.26-1.20)	0.66 (0.33-1.30)
Positive	14	8/14 (57)		
Negative	14	6/14 (43)		
P value		.71	.13	.23
EGFR			1.12 (0.50-2.54)	0.71 (0.33-1.51)
Wild type	20	6/18 (33)		
Mutation	9	8/9 (89)		
P value		.01	.78	.37
EGFR IHC				
Cytoplasm			0.46 (0.23-0.93)	0.40 (0.21-0.79)
0-200	25	6/17 (35)		
>200	19	9/14 (64)		
P value		.16	.03	.01
Membrane			0.35 (0.15-0.86)	0.24 (0.10-0.55)
0-200	32	7/20 (35)		
>200	12	8/11 (73)		
P value		.07	.02	.001
E-cadherin IHC			1.13 (0.55-2.32)	1.08 (0.56-2.07)
0-200	14	5/10 (50)		
>200	34	12/26 (46)		
P value		1.00	.74	.82

Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; FISH = fluorescent in situ hybridization; HR = hazard ratio; IHC = immunohistochemistry; OS = overall survival; PFS = progression-free survival; SWOG = Southwestern Oncology Group.

first-line therapy according to the presence of *EGFR* mutations but not BAC histologic features or the clinical factor of 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 trial of 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 showed a significantly longer median PFS (16.0 vs. 9.7 months) with the combination, with OS not yet reported.¹⁸ Additional supportive data have come from the single-arm European BELIEF (bevacizumab and erlotinib in *EGFR* mutation-positive NSCLC) trial of erlotinib with bevacizumab, which demonstrated efficacy far exceeding the 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 for patients in Europe with advanced NSCLC with an activating *EGFR* mutation.²⁰ In addition, a North American randomized phase II trial of erlotinib versus erlotinib/bevacizumab in *EGFR* mutation-positive NSCLC by the Academic and Community Cancer Research United 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 the SWOG 0635 trial. Although still

sometimes considered a distinct category of NSCLC by clinical oncologists, the new categorization of lung adenocarcinomas³ has redefined multifocal BAC as lepidic-predominant adenocarcinoma. Although BAC and adenoBAC were the descriptors used for the 0635 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 were unable to classify subsets of patients as having what was previously characterized as nonmucinous or mucinous BAC, because this feature was reported inconsistently.

Along with the fundamental redefinition of NSCLC that removed the BAC subgroup, the management of NSCLC has evolved since both these trials were developed and now follows an algorithm defined by the presence or absence of a driver mutation such as an *EGFR* gene mutation or several others. Just as for patients with a histologic type formerly identified as BAC or adenoBAC, never smokers now follow a treatment path based on the presence of an activating *EGFR* mutation or other biomarker.

No evidence was found of a significant difference in outcomes when stratified by the presence or absence of rash or hypertension, although the development of diarrhea was associated with significantly longer OS. In the absence of significant improvement in PFS, this observation is provocative but difficult to interpret without addressing this question in other data sets with *EGFR* TKIs. The favorable tolerability of this combination in both trial populations was also notable.

Paired Phase II Studies of Erlotinib/Bevacizumab for BAC and NSCLC

Molecular marker testing was very limited in S0635; thus, it is unknown whether markedly greater efficacy was limited to specific molecularly defined subgroups. However, our efforts to perform molecular characterization of patient tumors in the S0635 trial 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 BAC subtype,¹⁵ associated with a very low probability of significant benefit from EGFR TKI-directed therapies.¹⁶

The molecular marker correlates from the S0636 trial revealed that patients with tumors demonstrating high EGFR protein expression had superior OS and PFS compared with those patients with tumors having no or low EGFR protein expression, although only the association with PFS was statistically significant. Owing to the small number of patients, these results should be interpreted with caution, and a prognostic association cannot be ruled out. In larger studies of EGFR TKIs for NSCLC, the level of protein expression was not shown to be of significant predictive value.²²

Conclusion

Despite these limitations, the results from the S0635 and S0636 studies, taken together, have corroborated the conclusion that a subset of patients benefit from the 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 and the median OS of 13 months with gefitinib¹⁶ and 17 months with erlotinib² in this clinically defined population. Molecular marker testing was very limited in this multicenter trial; thus, it is unknown whether markedly greater efficacy was limited to specific molecularly defined subgroups. Similarly, although S0636 did not use molecular selection and is known to have included many patients without an *EGFR* mutation, the median OS of 29 months far exceeded our prospectively identified threshold for considerable interest of 19 months and was remarkable for a population not composed 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.

Clinical Practice Points

- Before the broad adoption of testing for *EGFR* mutations and molecular selection of patients to receive EGFR TKIs, clinically identified subsets of patients with advanced BAC and never smokers emerged as clinically selected subgroups particularly likely to benefit from these agents.
- Limited preclinical and clinical evidence support the combination of erlotinib and bevacizumab as potentially superior in efficacy to EGFR TKI therapy alone.
- OS, as the primary endpoint in paired phase II trials of these populations, was 21 and nearly 30 months for patients with advanced BAC and never smokers with advanced lung adenocarcinoma, respectively.
- Although the field has moved toward molecular selection to guide recommendations regarding which patients should receive EGFR TKI-based therapy, these data, obtained from clinically,

rather than molecularly, selected patient populations, are consistent with potentially superior activity of the erlotinib and bevacizumab combination for patients most likely to benefit from EGFR-directed therapy.

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Disclosure

The authors declare that they have no competing interests.

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