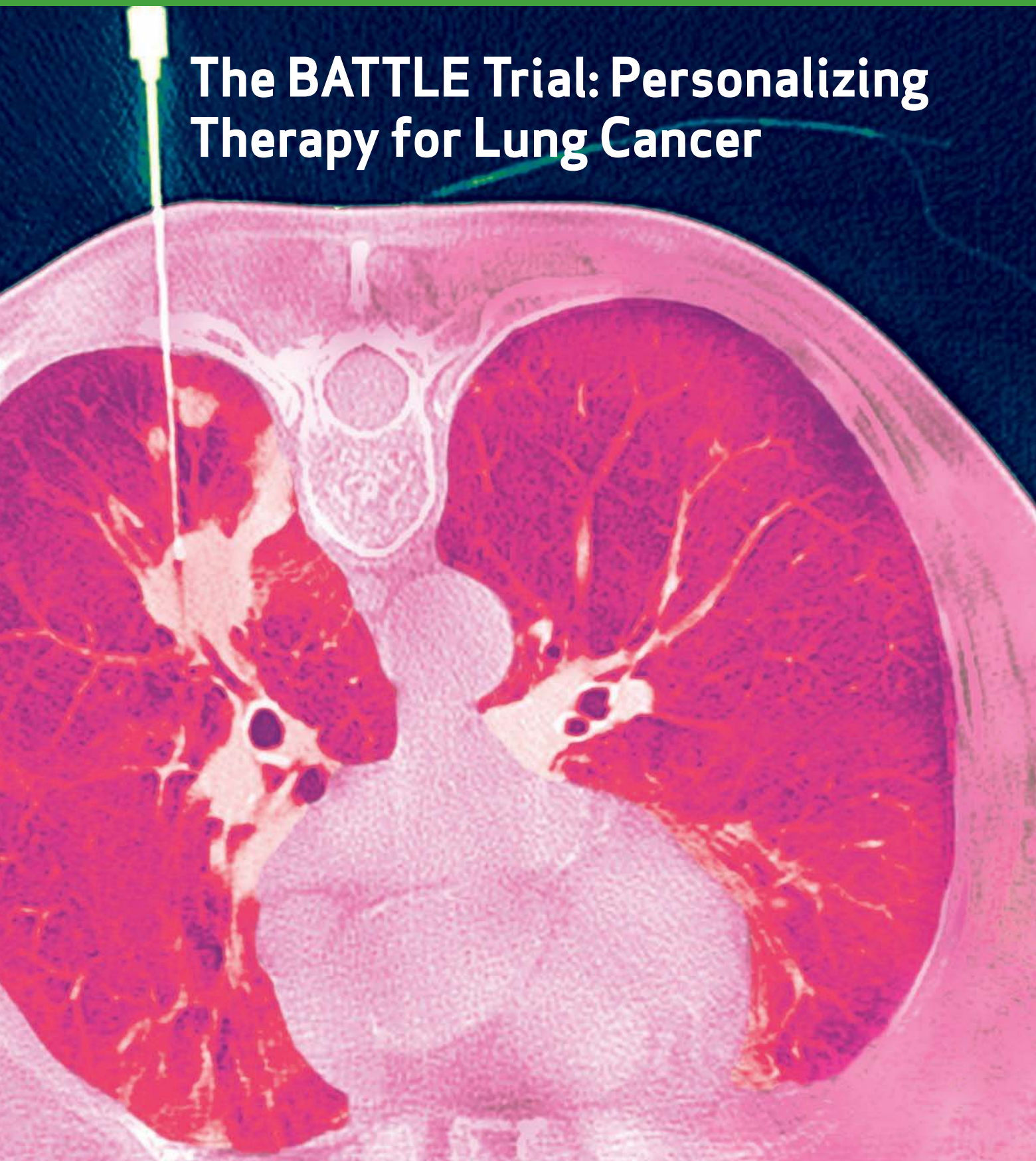
Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

RESEARCH ARTICLE

The BATTLE Trial: Personalizing Therapy for Lung Cancer



Edward S. Kim[1,], Roy S. Herbst[1,*], Ignacio I. Wistuba[1,2,*], J. Jack Lee[3,*], George R. Blumenschein Jr[1], Anne Tsao[1], David J. Stewart[1], Marshall E. Hicks[4], Jeremy Erasmus Jr[4], Sanjay Gupta[4], Christine M. Alden[1], Suyu Liu[3], Ximing Tang[1], Fadlo R. Khuri[5], Hai T. Tran[1], Bruce E. Johnson[6], John V. Heymach[1], Li Mao[7], Frank Fossella[1], Merrill S. Kies[1], Vassiliki Papadimitrakopoulou[1], Suzanne E. Davis[1], Scott M. Lippman[1,†], and Waun K. Hong[1,†]*

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

ABSTRACT

The Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial represents the first completed prospective, biopsy-mandated, biomarker-based, adaptively randomized study in 255 pretreated lung cancer patients. Following an initial equal randomization period, chemorefractory non–small cell lung cancer (NSCLC) patients were adaptively randomized to erlotinib, vandetanib, erlotinib plus bexarotene, or sorafenib, based on relevant molecular biomarkers analyzed in fresh core needle biopsy specimens. Overall results include a 46% 8-week disease control rate (primary end point), confirm prespecified hypotheses, and show an impressive benefit from sorafenib among mutant-*KRAS* patients. BATTLE establishes the feasibility of a new paradigm for a personalized approach to lung cancer clinical trials. *(ClinicalTrials.gov numbers: NCT00409968, NCT00411671, NCT00411632, NCT00410059, and NCT00410189.)*

SIGNIFICANCE: The BATTLE study is the first completed prospective, adaptively randomized study in heavily pretreated NSCLC patients that mandated tumor profiling with "real-time" biopsies, taking a substantial step toward realizing personalized lung cancer therapy by integrating real-time molecular laboratory findings in delineating specific patient populations for individualized treatment. *Cancer Discovery; 1(1); 44–53. ©2011 AACR.*

INTRODUCTION

The leading cause of cancer-related mortality, lung cancer accounts for more U.S. deaths each year than do breast, colon, prostate, liver, and kidney cancers and melanoma combined (1). Systemic chemotherapy is the mainstay for metastatic lung cancer. Although approved therapies in this setting include a few biologic agents, subjective physician preference based on clinical characteristics such as age, gender, or performance status largely drives treatment decisions (2–4).

Tumor biomarker evaluations have recently emerged as an important factor in planning treatment for non–small cell lung cancer (NSCLC) after improved outcomes with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) erlotinib and gefitinib in patients with NSCLC harboring *EGFR* mutations (5–8). Notwithstanding this success, biologic agents have not been effective in many randomized trials in NSCLC. There is a paucity of effective predictive markers of drug sensitivity or resistance, due in large part to difficulties in prospectively obtaining baseline tumor tissue in patients with metastatic NSCLC. In patients with pretreated NSCLC, tumor biomarker evaluation is frequently based on the tissue obtained at diagnosis and may not reflect the current state of biomarkers after treatment with chemotherapy.

In the novel phase II Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) program of personalized medicine (ClinicalTrials.gov numbers: NCT00409968, NCT00411671, NCT00411632, NCT00410059, and NCT00410189) reported in this article, we prospectively biopsied tumors and, based on tumor markers, used adaptive randomization to assign NSCLC patients to the treatment with greatest potential benefit based on cumulative data (Fig. 1). The signaling pathways and targeted

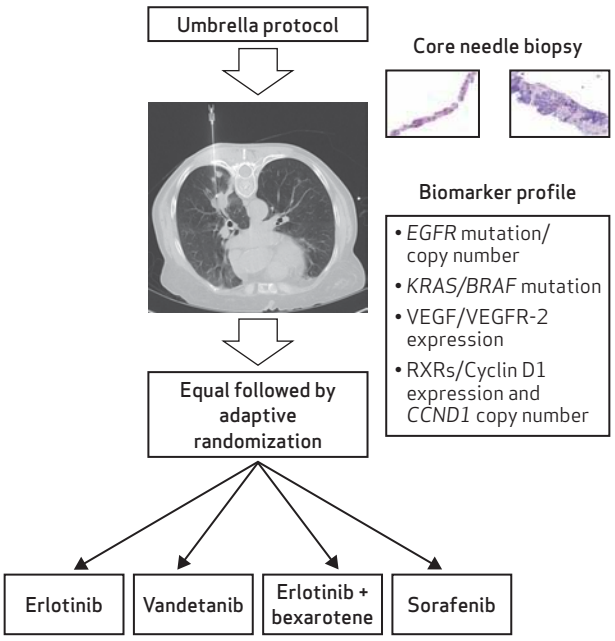


Figure 1. Schema for BATTLE study.

Authors' Affiliations: [1]Departments of Thoracic/Head and Neck Medical Oncology, [2]Pathology, [3]Biostatistics, and [4]Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [5]Winship Cancer Center, Emory University, Atlanta, Georgia; [6]Dana-Farber Cancer Institute, Boston, Massachusetts; and [7]University of Maryland, Baltimore, Maryland.

*These authors contributed equally to this article.

†These authors are co-senior authors of this article.

Note: Supplementary data for this article are available at Cancer Discovery Online (http://www.aacrjournals.org).

Corresponding Author: Waun K. Hong, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Phone: 713-794-1441; Fax: 1-713-792-4654; E-mail: whong@mdanderson.org

doi: 10.1158/2159-8274.CD-10-0010

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

agents were selected on the basis of the highest scientific and clinical interest at the time (2005) and included EGFR (erlotinib), KRAS/BRAF (sorafenib), retinoid–EGFR signaling (bexarotene and erlotinib), and vascular endothelial growth factor receptor [VEGFR; vandetanib (refs. 9–12)]. All of these compounds were being tested in the phase II or III setting and thus were appropriate for treatment of patients with advanced NSCLC. Testing the feasibility of performing core biopsy procedures in pretreated patients with advanced disease and utilizing real-time biomarker analyses for treatment were major challenges in BATTLE and, if successful, were proposed as major steps toward personalizing therapy for patients with NSCLC.

RESULTS

Patient Characteristics

A total of 341 patients were enrolled in the BATTLE study between November 30, 2006, and October 28, 2009, with equally random assignments for the first 97 patients and adaptive randomization for the remaining 158. The numbers of randomized patients per treatment arm were 59 (erlotinib), 54 (vandetanib), 37 (erlotinib plus bexarotene), and 105 (sorafenib). Seventeen patients were randomly assigned twice, and 1 patient 3 times. Eighty-six patients could not be randomly assigned because of intercurrent illnesses (n = 29) or worsening overall condition (n = 22), conditions preventing a biopsy (n = 17), or choice of an alternative treatment (n = 18; Fig. 2).

Notable patient characteristics included 83 patients (33%) with prior brain metastases, 116 (45%) with prior treatment with an EGFR TKI, and a median of 2 prior chemotherapies (Table 1). Our patient population was reflective of a heavily pretreated NSCLC population, with 44% (102 patients) having progression as their best response to prior therapy. Supplementary Table S1 lists the distribution of individual biomarkers. The prevalence of mutations in our study population included 15% *EGFR* and 20% *KRAS*. Forty-two patients had inadequate tissue for biomarker analysis, and 2 patients were negative for all study biomarkers.

Efficacy

The overall 8-week disease control rate (DCR) in 244 patients eligible for this analysis was 46% (Table 2); median progression-free survival (PFS) was 1.9 months [95% confidence interval (CI), 1.8–2.4]; median overall survival (OS) was 8.8 months (95% CI, 6.3–10.6); and 1-year survival was 35% (Supplementary Fig. S1). The median patient follow-up was 10.3 months. There were no complete responses and only

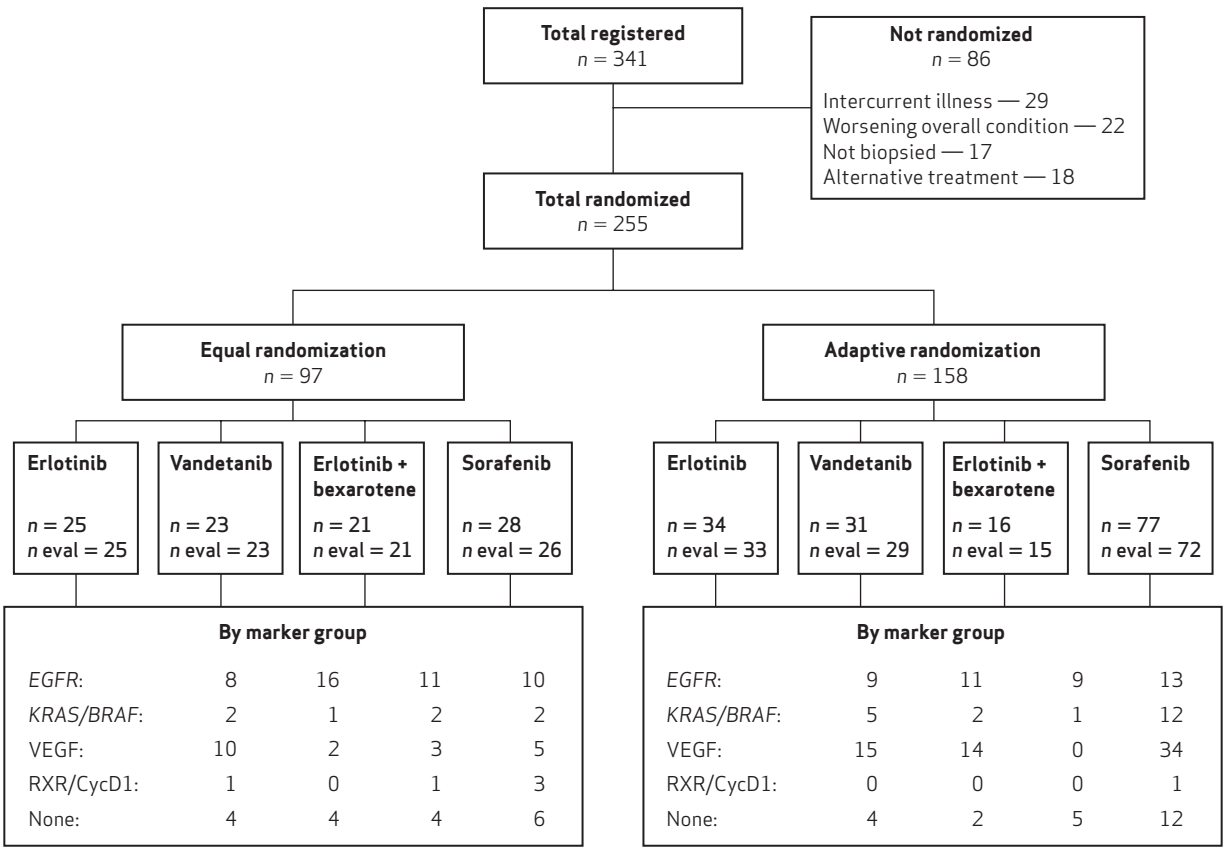


Figure 2. CONSORT diagram of the BATTLE study.

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

Table 1. Patient characteristics by treatment

		All	Erlotinib ($n = 59$)	Vandetanib ($n = 54$)	Erlotinib + bexarotene ($n = 37$)	Sorafenib ($n = 105$)
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Age	≤50	41 (16%)	5 (8%)	11 (20%)	6 (16%)	19 (18%)
(mean, 62; range, 26–84)	51–60	73 (29%)	23 (39%)	15 (28%)	11 (30%)	24 (23%)
	61–70	86 (34%)	19 (32%)	19 (35%)	11 (30%)	37 (35%)
	>70	55 (22%)	12 (20%)	9 (17%)	9 (24%)	25 (24%)
Gender	Female	118 (46%)	26 (44%)	29 (54%)	12 (32%)	51 (49%)
	Male	137 (54%)	33 (56%)	25 (46%)	25 (68%)	54 (51%)
Ethnicity	Caucasian	209 (82%)	51 (86%)	41 (76%)	31 (84%)	86 (82%)
	Hispanic	16 (6%)	2 (3%)	7 (13%)	0 (0%)	7 (7%)
	African American	16 (6%)	3 (5%)	2 (4%)	4 (11%)	7 (7%)
	Asian	14 (5%)	3 (5%)	4 (7%)	2 (5%)	5 (5%)
Smoker	Current	23 (9%)	9 (15%)	5 (9%)	3 (8%)	6 (6%)
	Former	177 (69%)	41 (69%)	31 (57%)	32 (86%)	73 (70%)
	Never	55 (22%)	9 (15%)	18 (33%)	2 (5%)	26 (25%)
Histology	Adenocarcinoma	160 (63%)	31 (53%)	35 (65%)	23 (62%)	71 (68%)
	Squamous	46 (18%)	16 (27%)	7 (13%)	6 (16%)	20 (19%)
	Others	49 (19%)	12 (20%)	12 (22%)	8 (22%)	14 (13%)
Prior erlotinib therapy	No	139 (55%)	59 (100%)	9 (17%)	37 (100%)	34 (32%)
	Yes	116 (45%)	0 (0%)	45 (83%)	0 (0%)	71 (68%)
ECOG performance status	0	22 (9%)	5 (8%)	9 (17%)	2 (5%)	6 (6%)
	1	197 (77%)	44 (75%)	36 (67%)	30 (81%)	87 (83%)
	2	36 (14%)	10 (17%)	9 (17%)	5 (14%)	12 (11%)
Prior cytotoxic chemotherapy	1	95 (37%)	25 (42%)	21 (39%)	18 (49%)	31 (30%)
(median, 2; range, 1–6)	2	84 (33%)	20 (34%)	17 (31%)	12 (32%)	35 (33%)
	3	40 (16%)	9 (15%)	7 (13%)	4 (11%)	20 (19%)
	4	24 (9%)	4 (7%)	6 (11%)	2 (5%)	12 (11%)
	5	9 (4%)	1 (2%)	2 (4%)	1 (3%)	5 (5%)
	6	3 (1%)	0 (0%)	1 (2%)	0 (0%)	2 (2%)

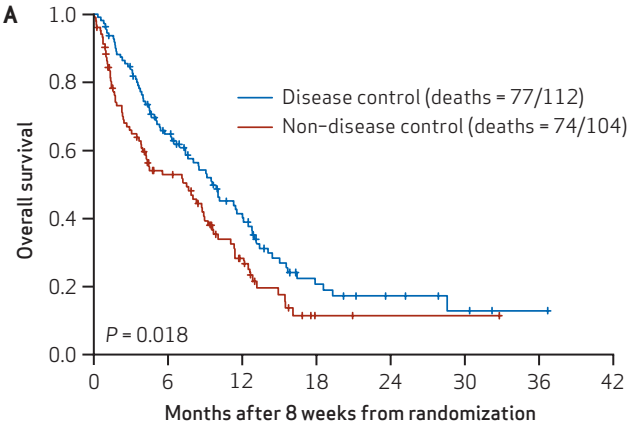
Table 2. Eight-week disease control status by treatment and marker groups

Number of patients with disease control / total number of patients (%)

Marker group	Treatment				Total
	Erlotinib	Vandetanib	Erlotinib + bexarotene	Sorafenib	
EGFR	6/17 (35%)	11/27 (41%)[a]	11/20 (55%)[a]	9/23 (39%)	37/87 (43%)
KRAS/BRAF	1/7 (14%)	0/3 (0%)	1/3 (33%)	11/14 (79%)[a]	13/27 (48%)
VEGF/VEGFR-2	10/25 (40%)[a]	6/16 (38%)	0/3 (0%)	25/39 (64%)[a]	41/83 (49%)
RXR/Cyclin D1	0/1 (0%)	0/0 (NA)	1/1 (100%)[a]	1/4 (25%)	2/6 (33%)
None	3/8 (38%)	0/6 (0%)	5/9 (56%)[a]	11/18 (61%)[a]	19/41 (46%)
Total	20/58 (34%)	17/52 (33%)	18/36 (50%)	57/98 (58%)	112/244 (46%)

[a] Cells showing effective treatments within specific marker groups defined as the probability of DCR given data is 80% or greater. Only 1 patient in the RXR/CycD1 marker group received erlotinib + bexarotene.

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010



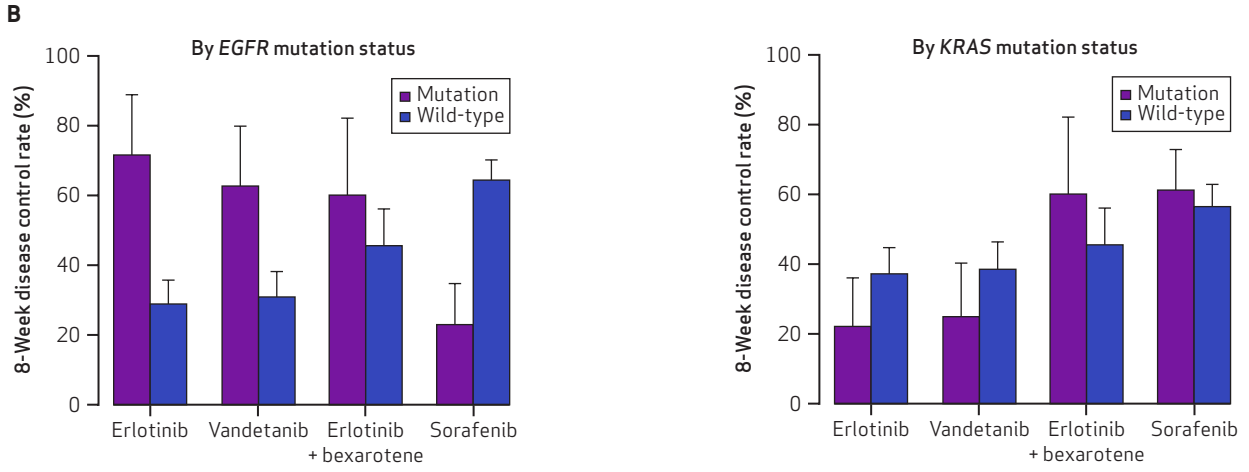


Figure 3. Major efficacy results of BATTLE study. **A**, landmark analysis of overall survival for patients with or without 8-week disease control. The landmark time point is set at 8 weeks; i.e., time 0 is at 8 weeks after randomization. **B**, 8-week disease control rates (in %) by treatment in patients with tumors harboring wild-type or mutated *EGFR* (left) and *KRAS* (right) genes.

9 partial responses in these heavily pretreated patients. In an 8-week landmark analysis, the median survival of patients with 8-week disease control (DC) was 9.6 months (95% CI, 7.4–12.5), compared with 7.5 months (95% CI, 4.2–9.2) for patients without 8-week DC (Fig. 3A; $P = 0.018$). The overall 8-week DCRs were 34% (erlotinib), 33% (vandetanib), 50% (erlotinib plus bexarotene), and 58% (sorafenib). Effective treatment–marker-group pairings, defined as having a 0.8 posterior probability of exceeding a DCR of 30%, were as follows: erlotinib in the VEGF/VEGF receptor 2 (VEGFR-2) group; vandetanib in the *EGFR* group; erlotinib plus bexarotene in the *EGFR*, retinoid X receptor (RXR)/Cyclin D1, and no-marker groups; and sorafenib in the *KRAS/BRAF*, VEGF/VEGFR-2, and no-marker groups (Table 2).

In addition to analysis of prespecified marker groups, we also studied effects of individual markers on treatment efficacy. In confirmation of our prespecified scientific hypotheses, individual markers that predicted a better 8-week DC of treatment [versus the marker's opposite status (absence or presence)] were *EGFR* mutations for erlotinib ($P = 0.04$), high VEGFR-2 expression for vandetanib ($P = 0.05$), and high Cyclin D1 expression for erlotinib plus bexarotene ($P = 0.01$). Exploratory predictive marker analysis results were as follows: a better 8-week DC with *EGFR* amplification for erlotinib plus bexarotene ($P = 0.006$); a worse 8-week DC with *EGFR* mutation ($P = 0.01$) or high *EGFR* polysomy ($P = 0.05$) for sorafenib; and, compared with the combined other treatments, sorafenib had a higher DCR (64% versus 33%) in *EGFR*–wild-type patients ($P < 0.001$) and a non-statistically significant trend toward better DCR (61% versus 32%) in mutant-*KRAS* patients ($P = 0.11$; Fig. 3B). In addition, in the *KRAS/BRAF* marker group, sorafenib had a 79% DCR compared to a 14% DCR with erlotinib ($P = 0.016$).

Toxicity

All 4 treatments were well tolerated, each having toxicity consistent with prior reports. Treatment-related grade 3–4 toxicity was 6.5% (Supplementary Table S2). Average compliance in each arm was >95%. Sorafenib produced the most toxicity, which caused discontinuation of treatment in 19% and dose reductions in 21% of sorafenib-treated patients (Supplementary Table S3). Lung biopsy was well tolerated by the 139 patients who underwent the procedure, with pneumothorax in 11.5%, and only 1 grade 3 event, which required overnight hospitalization.

DISCUSSION

The phase II randomized BATTLE trial made important clinical discoveries and demonstrated the feasibility of its novel design for advancing personalized treatment of NSCLC. BATTLE is the first completed prospective, biopsy-mandated, biomarker-based, adaptively randomized clinical study in patients with pretreated, advanced lung cancer. The trial data validated prespecified scientific hypotheses

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

regarding predictive biomarkers for targeted agents and identified potential new predictive markers. The BATTLE study is important in demonstrating several key points: 1) establishing the feasibility of performing biopsies and real-time biomarker analyses in previously treated lung cancer patients; 2) identifying interactions between the treatments and markers (e.g., DCR of 79% with sorafenib but only 14% with erlotinib in the *KRAS/BRAF* marker group) for guiding adaptive randomization; and 3) confirming the prespecified hypotheses of treatment efficacy in the presence of individual markers related to the treatments' mechanism of action.

EGFR mutations have been adopted as a predictive biomarker for directing NSCLC patient treatment with EGFR TKIs but are present in only 10% to 15% of the lung cancer population. Results from the vast majority of chemotherapy-based clinical trials in NSCLC, which continue to treat NSCLC as a homogeneous disease, have been disheartening, and personalized trials targeting molecular NSCLC characteristics of individual patients may be a viable option for improving treatment outcomes.

We showed that 8-week DC status is a good surrogate for OS in previously treated patients, as also reported by the Southwest Oncology Group during BATTLE (13). This clinically relevant, short-term, surrogate end point facilitated the rapid integration of outcome data into adaptive randomization, confirming its utility for personalizing treatment assignments. In addition, the short-term nature of the 8-week DC end point was not considered to be affected by patients who had received multiple prior treatments before BATTLE. Our overall response rate of 4% is reflective of a heavily pretreated NSCLC population and consistent with other published studies in this population (5, 9, 14).

Results of the BATTLE study support the potential of various biomarkers to predict the sensitivity or resistance of patients to targeted agents. Sorafenib was active against tumors with mutated or wild-type *KRAS*, but had a worse DCR (compared with other study agents) in patients with *EGFR* mutations. As expected (5–7, 15–17), erlotinib was beneficial in patients with mutated-*EGFR* tumors. Erlotinib plus bexarotene improved DC in patients with a higher expression of Cyclin D1, suggesting a potential role for bexarotene in lung cancer treatment (11); similar to sorafenib, the combination also improved DC in the *KRAS*-mutant patient population. Future randomized, controlled studies are needed to further confirm the predictive value of these biomarkers. These findings (e.g., association of increased expression of Cyclin D1 with benefit from treatment with bexarotene and erlotinib, and sorafenib's activity in patients with both *KRAS*-mutant and *KRAS*–wild-type tumors) have fueled enthusiasm to further test these compounds in future clinical trials.

Biomarker profiles may differ between early-stage and advanced lung tumors. In current practice, biomarker profiles are determined from the original diagnostic tissue and may not reflect the current tumor biomarker status after receiving treatments, thus hampering decision making for personalized treatment. The present study performed real-time biopsies for assessing the current status of tumor biomarkers in patients, thus validating the feasibility of this paradigm-shifting approach.

The BATTLE approach could be expanded to develop personalized cytotoxic therapy. ERCC1 or RRM1 protein overexpression can help direct cytotoxic therapy, but these markers are not widely used in the clinical setting; other cytotoxic-therapy markers need further elucidation (18, 19). We mandated at least 2 core needle biopsies (CNB) in BATTLE and collected additional tissue and blood for discovering new biomarkers, including gene signatures, which may help further define patient populations sensitive to specific cytotoxic and biologic treatments.

Our study has some important limitations. First, and probably most important, our biomarker groups were less predictive than were individual biomarkers, which diluted the impact of strong predictors in determining treatment probabilities. For example, *EGFR* mutations were far more predictive than was the overall *EGFR* marker group. The unfortunate decision to group the EGFR markers also impacted the other marker groups and their interactions with other treatments, resulting in a suboptimal overall DCR as described. Second, several of the prespecified markers (e.g., RXR) had little, if any, predictive value in optimizing treatment selections. This limitation will be addressed in future studies by not grouping or prespecifying biomarkers prior to initiating these biopsy-mandated trials. In addition, adaptive randomization, which assigns more patients to the more effective treatments within each biomarker group, only works well with a large differential efficacy among the treatments (as evident in the *KRAS/BRAF* group), but its role is limited without such a difference (e.g., in the other marker groups). Allowing prior use of erlotinib was another limitation and biased treatment assignments; in fact, the percentage of patients previously treated with erlotinib steadily increased during trial enrollment. Overall, 45% of our patients were excluded from the 2 erlotinib-containing arms because of prior EGFR TKI treatment. As erlotinib is a standard of care therapy in NSCLC second-line, maintenance, and front-line settings, the number of patients receiving this targeted agent will likely continue to increase.

The BATTLE approach requires a highly integrated team of multidisciplinary investigators and should be implemented at specialized centers in carefully designed clinical trials. However, once a validated biomarker predicting benefit of treatment is identified, conducting this type of study in both academic and community environments will help promote the use of biomarkers to select patients for optimal treatment assignments.

While proving that the BATTLE-type platform is feasible, we have also learned several important lessons from our initial experience that have and will impact the design and conduct of future BATTLE studies focused on pretreated NSCLC populations. A forthcoming study (BATTLE-2) of targeted agents in pretreated patients with advanced NSCLC will further refine our experience with this approach. In BATTLE-2, we prespecify an extremely limited set of markers and will use the first half of the study population (approximately 200 patients) to conduct prospective testing of biomarkers/signatures. Upon completing this analysis, the "best" (most predictive) markers and signatures will be used to guide patient assignments to the most favorable matched treatments in the second half of the study (approximately 200 patients). Patients enrolled would be screened for *EGFR* mutations and *ALK*

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

translocations (20). If positive, they would not be eligible for enrollment in this study but would be referred to other ongoing trials testing agents targeting those mutations. We believe this is an ethical design and would allow patients to be exposed to additional novel therapies for lung cancer treatment.

BATTLE is the first completed prospective, adaptively randomized study in heavily pretreated NSCLC patients that mandated tumor profiling with real-time CNBs, demonstrating the feasibility of this approach and creating a new paradigm for translational research. This trial took a substantial step toward realizing personalized lung cancer therapy by integrating real-time molecular laboratory findings in delineating specific patient populations for individualized treatment. BATTLE accumulated increasing probabilities of a positive treatment outcome and showed the potential of its mandatory-biopsy design for developing specific predictive biomarkers and associated treatments for subsequent definitive clinical testing. This approach will be important for future evaluations of new molecular targets and predictive biomarkers (21–23). The successful completion of BATTLE reported in this article will potentially facilitate the implementation of future trials of personalized treatments in lung and other cancers with even more efficient designs, as a forerunner in the quest for discovery of novel cancer treatments.

METHODS

Patient Population

We recruited patients with pretreated NSCLC at the University of Texas MD Anderson Cancer Center (MDACC) who agreed to a baseline tumor biopsy procedure. Eligibility also included age ≥18 years and adequate performance status (ECOG grade 0–2). Prior treatment with erlotinib was allowed, but such patients were excluded from the erlotinib-containing study arms, and stable (for at least 4 weeks) or treated brain metastases were permitted. Patients with multiple lines of prior therapy were eligible if they had adequate performance status. Radiographic imaging of tumors was reviewed to determine suitability for biopsy. All participants provided written informed consent. Other eligibility criteria appear in the Supplementary Data.

Study Design

BATTLE was a randomized phase II, single-center, open-label study in patients with advanced NSCLC refractory to prior chemotherapy (Fig. 1). Following molecular tumor-biomarker assessments, patients were randomly assigned to oral treatment with erlotinib (150 mg once daily; Tarceva, OSIP/Genentech), vandetanib (300 mg once daily; Zactima, AstraZeneca), erlotinib (150 mg once daily) plus bexarotene (400 mg/m^2 once daily; Targretin, Eisai), or sorafenib (400 mg twice daily; Nexavar, Bayer/Onyx). The primary end point was the DCR at 8 weeks. Secondary end points included response rate, PFS, OS, and toxicity. Planned exploratory objectives were each treatment's efficacy in relation to patient biomarker profiles.

The Institutional Review Boards of MDACC and the U.S. Department of Defense approved the study, which was monitored by an independent Data and Safety Monitoring Board.

Biopsy, Molecular Analysis, and Biomarker Grouping

An interventional radiologist used computed tomography or ultrasound guidance to obtain fresh CNB tumor specimens from each patient (Supplementary Data). The procedure yielded 1 to 3 tissue cores approximately 1 mm in diameter and 1.2 to 1.8 cm long (average length, 1.5 cm). Each CNB specimen was divided at collection into 2 portions: 1) tissue for clinical-trial biomarker analysis (at least 1 core), and 2) tissue for future gene expression and proteomic biomarker analysis (at least 1 core). A critical study aspect was the concurrent collection of additional CNB tissue samples, which were prepared simultaneously with the study specimens, for future discovery of novel biomarkers.

The CNB tissue specimens designated for clinical-trial biomarker analysis were formalin-fixed immediately in the interventional radiology suite and transported to the research laboratory for processing and subsequent histologic and biomarker analyses. Molecular pathologist I. Wistuba (MDACC) reviewed formalin-fixed, paraffin-embedded, and hematoxylin-and-eosin (H&E)–stained histologic sections within 24 hours of collection to assess the presence, quantity, quality, and histologic type of tumor tissue. Each histology section considered adequate for biomarker analysis had ≥200 malignant cells.

Tumor specimens from the mandatory CNB procedure (minimum of 2 cores; see Supplementary Data) were tested for the following 11 prespecified biomarkers: mutations of *EGFR*, *KRAS*, and *BRAF*; copy numbers (by FISH) of *EGFR* and the *Cyclin D1* gene (*CCND1*); and protein expression levels of VEGF, VEGFR-2, RXRs α, β, and γ, and Cyclin D1. The MDACC Thoracic Molecular Pathology Research Laboratory performed these biomarker tests (see Supplementary Data), reporting results within 2 weeks of each biopsy procedure. Biomarker choices and criteria for classifying each biomarker test as positive or negative were prespecified prior to starting this study on the basis of data available in 2005 (15–17, 24, 25). Patients and investigators were blinded to the biomarker results until the patient was taken off the study.

Five biomarker groups were established and ranked for predictive value (based on evidence available at trial initiation) from 1 (highest) to 5 (lowest), as follows: 1) *EGFR* mutation and/or *EGFR* amplification/high polysomy; 2) *KRAS* or *BRAF* mutation; 3) VEGF and/or VEGFR-2 overexpression; 4) RXR α, β, or γ overexpression and/or Cyclin D1 overexpression and/or *CCND1* amplification; or 5) no study biomarkers. Each patient was assigned to one of these groups; patients with biomarkers in more than one group were assigned to the group with the highest ranking. Our prespecified hypothesis was that each treatment regimen would be efficacious for patients presenting markers related to the treatment's mechanism of action. Namely, erlotinib, sorafenib, vandetanib, and erlotinib plus bexarotene would work for patients with *EGFR* mutation/amplification, *KRAS* or *BRAF* mutation, VEGF and/or VEGFR-2 overexpression, and RXR receptor overexpression and/or Cyclin D1 overexpression/amplification, respectively.

Biopsy Procedure

Written informed consent was obtained from each patient before each biopsy. Coagulopathies were corrected prior to biopsy. All biopsies were performed under computed tomographic or sonographic guidance by a board-certified interventional radiologist with the patient in the prone, supine, or lateral decubitus position, depending on the location of the lesion. During the biopsy, patients received either local anesthesia or monitored, moderate sedation. Patients' skin was aseptically prepared and draped, and 1% lidocaine was administered subcutaneously for local anesthesia. A coaxial biopsy technique was used for all patients. With image guidance to evaluate the needle's trajectory, an 18- or 19-gauge guide needle (Cook) was inserted through the skin and advanced to a position close to the target lesion. After imaging confirmation of the needle tip's position, 2 or 3 core biopsy samples were obtained with a 20-gauge biopsy needle (Quick-core; Cook). The samples were handed over to the appropriate research personnel for handling and processing.

After the biopsy procedure, patients were monitored by the nursing staff in the radiology department's recovery area. In patients

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

who underwent a lung or mediastinal biopsy, an upright inspiratory posteroanterior chest radiograph was obtained within 30 minutes of the biopsy procedure. In the absence of a pneumothorax, the procedure included a second chest radiograph 3 hours after the biopsy. If the initial chest radiograph showed a pneumothorax, a follow-up radiograph was obtained after 1 hour. Chest tubes were inserted if the pneumothorax size was >30%, the pneumothorax increased in size, or patients experienced pain, shortness of breath, or a decrease in oxygen saturation.

Biomarker Methodology

To evaluate 11 molecular biomarkers (Supplementary Table S1) using the formalin-fixed paraffin-embedded (FFPE) CNB tissue specimens, 13 5-μm histology sections were obtained, as follows: 1) H&E histology analysis (n = 1 section); 2) DNA extraction for mutation analyses (*EGFR*, *KRAS*, and *BRAF*; n = 1 or 2 sections); 3) FISH analysis (*EGFR* and *CCND1*; n = 2 sections); and 4) immunohistochemistry (IHC) analysis (VEGF, VEGFR-2, Cyclin D1, RXRα, RXRβ, and RXRγ; n = 6 sections). All specimens were assigned an identification number linked to the clinical trial identification number for subsequent processing in the laboratory. Certification of the presence of adequate tumor tissue in the FFPE tissue specimens by histologic examination was performed within 24 to 48 hours, and analysis of the 11 molecular biomarkers was performed, completed, and reported, in most cases, within 14 days.

Microdissection and DNA extraction Malignant tumor cells were manually microdissected from 4 sequential 5-μm-thick H&E-stained FFPE histology sections. DNA was extracted using 25 μL of Pico Pure TM DNA Extraction solution (Arcturus) containing proteinase K and incubated at 65°C for 24 hours. Subsequently, proteinase K inactivation was performed by heating samples at 95°C for 10 minutes.

Mutation analysis Mutations of *EGFR* (exons 18–21), *KRAS* (exons 1, codons 12 and 13; and exon 2, codon 61), and *BRAF* (exons 11 and 15) were studied using DNA extracted from microdissected FFPE tumor cells. The DNA sequences were PCR amplified using primers shown in Supplementary Table S1. Each PCR amplification was performed in 30 μL of volume containing 2 μL of DNA (approximately 100 ng of genomic DNA), 0.3 of μM forward and reverse primers, and 15 μL of HotStarTaq (1.5 units of DNA polymerase) Master Mix (Qiagen) for 40 cycles at 94°C for 30 seconds, for 30 seconds at the primer pairs' annealing temperature (Supplementary Table S1), and at 72°C for 45 seconds, followed by 7 minutes of extension at 72°C. All PCR products were directly sequenced using Applied Biosystems PRISM dye terminator cycle sequencing method (Perkin-Elmer). All sequence variants were confirmed by independent PCR amplifications from at least 2 independent DNA extractions, and sequenced in both directions.

EGFR and CCND1 copy number analysis Copy number of both genes was analyzed using FISH. For *EGFR*, gene copy number per cell was analyzed using the LSI EGFR SpectrumOrange/CEP7 SpectrumGreen Probe (Abbott Molecular), as previously described (16). For *CCND1*, the Vysis LSI *CCND1* (SO)/CEP11 DNA probe set (Abbott Molecular) was used. For both FISH analyses, histology sections were incubated at 56°C overnight and deparaffinized by washing in CitriSolv (Fisher Scientific). After incubation in denaturing solution containing 70% formamide and 2× SSC buffer, pH 7.0, at 73°C for 5 minutes, the histology sections were digested with proteinase K (0.25 mg/mL in 2× SSC) at 37°C for 15 to 25 minutes, rinsed in 2 × SSC (pH 7.0) at room temperature for 5 minutes, and dehydrated using ethanol in a series of increasing concentrations (70%, 85%, 100%). The probe set was applied onto the selected area, per the manufacturer's instructions, on the basis of the tumor foci seen on each slide. The hybridization area was covered with a glass coverslip and then sealed with rubber cement. The slides were incubated at 80°C for 10 minutes for co-denaturation of chromosomal and probe DNA and then placed in a humidified chamber at 37°C for 20 to 24 hours to allow hybridization to occur. Posthybridization washes were performed in 1.5-M urea and 0.1× SSC (pH, 7.0–7.5) at 45°C for 30 minutes and in 2× SSC for 2 minutes at room temperature. After the samples were dehydrated in a series of increasing ethanol concentrations, 4',6'-diamidino-2-phenylindole (0.15 mg/mL) in Vectashield Mounting Medium (Vector Laboratories) was applied for chromatin counterstaining.

For both genes, fluorescence signals were scored in at least 50 nonoverlapping interphase nuclei per tumor, and the section of the area was guided by images of the H&E-stained section. The number of copies of *EGFR* and chromosome 7 probes was assessed independently using a fluorescence microscope (Cytovision platform, Genetix). The number of copies of *CCDN1* and chromosome 11 probes was assessed independently using a fluorescence microscope (Cytovision platform, Genetix).

For *EGFR*, cases were classified into 6 FISH strata according to the frequency of cells with the *EGFR* gene copy number and referred to the chromosome 7 centromere, as follows: 1) disomy (≤3 copies in <10% of cells); 2) low trisomy (3 copies in 10%–40% of cells, 4 copies in <10% of cells); 3) high trisomy (3 copies in >40% of cells, 4 copies in <10% of cells); 4) low polysomy (≥4 copies in 10%–40% of cells); 5) high polysomy (≥4 copies in 40% of cells); and 6) gene amplification (ratio of *EGFR* gene to chromosome ≥2, presence of tight *EGFR* gene clusters and 15 copies of *EGFR* per cell in 10% of the analyzed cells). The high polysomy and gene amplification categories were considered to be high *EGFR* copy number, and the other categories were considered to be nonincreased *EGFR* copy number, as previously published (24, 26).

For *CCDN1*, cases were considered to have gene copy number gain when the average ratio of *CCND1* copy number to chromosome 11 centromere copy number was >1, or when clusters of *CCND1* signals were observed in >20% of nuclei, as previously published (27).

IHC analysis Protein expression of VEGF, VEGFR-2, RXRα, RXRβ, RXRγ, and Cyclin D1 was determined by IHC. For VEGF, VEGFR-2, RXRα, RXRβ, and RXRγ proteins, combined expression of cytoplasmic and membrane staining was assessed, and for RXRα and Cyclin D1 proteins, expression of nuclear staining was examined. Commercially available antibodies were used, as follows: VEGF, rabbit polyclonal antibody (Santa Cruz Biotechnology, Inc.), dilution 1:200; VEGFR-2, mouse monoclonal antibody (Santa Cruz Biotechnology, Inc.), dilution 1:200; RXRα, rabbit polyclonal antibody (Santa Cruz Biotechnology, Inc.), dilution 1:300; RXRβ, rabbit polyclonal antibody (Upstate), dilution 1:100; RXRγ rabbit polyclonal antibody (Santa Cruz Biotechnology, Inc.), dilution 1:200; and Cyclin D1, rabbit monoclonal antibody (clone SP4; Thermo Scientific), dilution 1:100.

All immunostaining was performed using automated stainers (DakoCytomation). Sections 5-μm thick were deparaffinized, rehydrated, and washed with PBS. Antigens were retrieved with 0.01-M citrate buffer (pH 6.0; DakoCytomation) for 30 minutes in a steamer. Samples were blocked for endogenous activity in 3% hydrogen peroxide-PBS, avidin–biotin solution (Zymed), and serum-free protein block (DakoCytomation) before incubation at room temperature with the primary antibody for 60 minutes for VEGF, RXRα, and RXRγ, and 65 minutes for VEGFR-2, RXRβ, and Cyclin D1. The sections were then washed in Tris-buffered saline (pH 7.4) and incubated with goat antirabbit biotinylated immunoglobulin (DakoCytomation). After incubation with the secondary antibody, the sections were incubated with the avidin-biotin-peroxidase complex (DakoCytomation) and developed with 3, 3′-diaminobenzidine. The sections were then rinsed in distilled water, counterstained with Mayer's hematoxylin,

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

and mounted for evaluation. Surgically resected FFPE NSCLC tumor tissue specimens with known expression of the markers were used as positive controls. The same FFPE tissues processed without the primary antibody were used as negative controls.

Biomarker scoring For VEGF, VEGFR-2, RXRα, RXRβ, and RXRγ proteins, combined expression of cytoplasmic and membrane staining was assessed, and for RXRα and Cyclin D1 proteins, expression of nuclear staining was examined. All expression was assessed using semiquantitative analysis of intensity and extension. For cytoplasmic/membrane expression, the percentage of positive tumor cells in the cytoplasm/membrane (0%–100%) was multiplied by the intensity of staining (0–3); therefore, the possible overall score ranged from 0 to 300. Cytoplasmic and membrane expression scores >100 were considered positive for VEGF and VEGFR-2, and scores >200 were considered positive for RXRβ and RXRγ. Nuclear expression was evaluated for any positive immunostaining, which was expressed in percentage. A nuclear score >30% was considered positive for RXRα, and a nuclear score >10% was considered positive for Cyclin D1.

Serum Collection

Samples were collected from consenting patients at baseline and after each cycle of treatment. Venous blood was collected at the following time points: baseline (pretreatment), end of cycles 1 and 2, and every 2 cycles thereafter until the patient went off protocol. At each time point, 8 mL of venous blood was collected into an EDTA-based Vaccutainer and plasma was separated via centrifugation, 1500 RPM for 15 minutes at 4°C within 30 minutes of collection. The resultant plasma was aliquoted into 3 prelabeled cryovials and stored at −70°C until analysis.

Statistical Analysis

The accrual goal was 250 randomized patients to achieve a sample size of 200 evaluable patients with complete marker profiles, which would allow an 80% power, with a 20% type I error rate, to identify effective treatments within each marker group. A high type I error rate prevented missing any potentially effective treatments that could be confirmed in larger, future studies (28).

The primary end point was the 8-week DCR [complete or partial response or stable disease via Response Evaluation Criteria in Solid Tumors (RECIST) (29)], which we compared with the historical 30% DCR estimate in similar patients (14). Treatment efficacy (a positive finding) was defined as >0.80 probability of achieving >30% DCR.

The statistical design was based on adaptive randomization under a Bayesian hierarchical model that would increasingly assign patients into treatments with the greatest potential for efficacy based on individual biomarker profiles (28). We planned to randomly assign at least the initial 80 patients equally to the 4 treatments, to allow at least 1 patient in each marker group to complete treatment, thus providing sufficient data to estimate the prior probability of DC for subsequent patients. Subsequent randomization "switched" to an adaptive algorithm, which incorporated the data of each patient evaluated at the 8-week time point (treatment, biomarker group, and 8-week DCR) into recalculations of the posterior probability of efficacy for treatments in relation to biomarker groups. This scheme adapts randomization probabilities for each of the 4 treatments from an equal chance, that is, 25% per treatment, to chances determined by biomarkers of >25% (high predicted DC) or <25% (low predicted DC).

Bayesian adaptive randomization bases treatment assignments on accumulating data within the trial, allowing more patients to be assigned to more effective therapies and fewer patients to be assigned to less effective therapies. This "learn-as-we-go" approach leveraged accumulating patient data to improve the treatment outcome. This trial design also allows the suspension of underperforming treatments in marker groups, as stipulated for our trial if the probability of a DCR >50% was <0.1 (detailed statistical assumptions can be found in ref. 28). The study was not designed to test the efficacy of equal versus adaptive randomization in improving DCR.

Standard statistical methods included the Fisher's exact test for contingency tables and log-rank test for survival data, in addition to calculating the Bayesian posterior probability. Each randomized patient represented a unit of the analysis. Time-to-event end points (e.g., OS) were censored at the time of a subsequent randomization for patients randomly assigned more than once.

Randomization

After categorization into marker groups, patients were randomly assigned to 1 of the 4 treatment arms. The initial cohort of eligible patients was randomly assigned to the 4 arms without regard to their respective marker groups (except for patients who had prior treatment with erlotinib, who were excluded from the 2 erlotinib-containing arms). These patients were assessed for associations between their marker groups and DC, giving a "prior" probability of the DCR for a given treatment in a given marker group. Patients enrolled after the initial cohort were randomly assigned to treatment according to a Bayesian adaptive algorithm, which incorporated the prior probability and DC data into a "posterior" probability of the DCR for a given treatment; the resulting posterior probability was continually updated per accumulating data on the associations between the DC and biomarkers of patients.

Clinical Assessments

Patients were evaluated clinically at the end of each treatment cycle (defined as lasting 4 weeks), and underwent imaging studies every 2 cycles, or every 8 weeks. Patients who progressed could reenter the clinical trial and be reassigned randomly to treatment if still eligible and agreeable to a new biopsy.

A radiologist independently assessed DC, which was defined as a complete or partial response or stable disease according to the RECIST (29) at the end of 8 weeks (start of treatment to end of second treatment cycle). PFS was assessed from the date of randomization to the earliest sign of disease progression or death from any cause. OS was assessed from the date of randomization until death from any cause. Tumor response was assessed every 8 weeks until disease progression. Toxicity was assessed in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Disclosure of Potential Conflicts of Interest

A. Tsao received commercial research support from Bristol-Myers Squibb, Merck, and Novartis and served on the advisory board for Genentech and Roche; B. Johnson served as consultant for AstraZeneca, Genentech, and Pfizer; D. Stewart received honoraria from AstraZeneca; E. Kim received commercial research support from AstraZeneca and Genentech and served as a consultant for AstraZeneca, Bayer, and Genentech; G. Blumenschein received commercial research support from Amgen, Bayer, Exelixis, GlaskoSmithKline, and Pfizer and served as a consultant for Amgen, Bayer, and GlaskoSmithKline; J. Heymach received commercial research support and served on the advisory board for AstraZeneca; I. Wistuba received commercial research support from AstraZeneca, Genentech, and Pfizer; R. Herbst received commercial research support and served as a consultant for AstraZeneca and Genentech; and V. Papadimitrakopoulou served on the advisory boards of Amgen and GlaxoSmithKline.

Acknowledgments

We gratefully acknowledge the patients who participated in the study, as well as Jeffrey Lewis for programming and database management support; Dawn Chalaire and Sunita Patterson for editorial assistance;

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010

the Faith, Family and Friends Foundation; Rexanna's Foundation; Mayberry Memorial Foundation; Stading Family Foundation; Hewett Foundation; Cohen-Reinach Family Charitable Foundation; and the National Foundation for Cancer Research. We also thank the MD Anderson Data Safety and Monitoring Board chaired by Dr. Donald A. Berry for monitoring the trial.

Grant Support

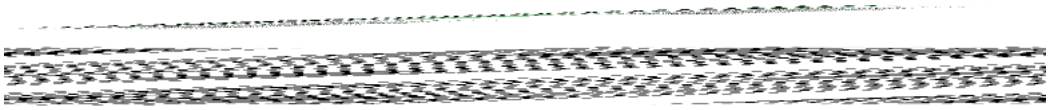
This research was supported in part by the Department of Defense Grant W81XWH-6-1-0303 and by the National Institutes of Health through MD Anderson's Cancer Center Support Grant P30 CA016672.

Received September 28, 2010; revised December 2, 2010; accepted December 20, 2010; published OnlineFirst April 3, 2011.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60:277–300.
2. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med 2008;359:1367–80.
3. Sandler A, Gray R, Perry MC, Brahmer H, Schiller JH, Dowlati, A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.
4. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543–51.
5. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small cell lung cancer (INTEREST): a randomized Phase III trial. Lancet 2008;372:1809–18.
6. Douillard JY, Shepherd FA, Hirsh V, Mok T, Socinski MA, Gervais R, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized Phase III INTEREST trial. J Clin Oncol 2010;28:744–52.
7. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
8. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958–67.
9. Shepherd FA, Pereira JR, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non–small-cell lung cancer. N Engl J Med 2005;353:123–32.
10. Schiller JH, Lee JW, Hanna NH, et al. A randomized discontinuation phase II study of sorafenib versus placebo in patients with non-small cell lung cancer who have failed at least two prior chemotherapy regimens: E2501. J Clin Oncol 2008;26(May 20 Suppl; abstr 8014)
11. Dragnev KH, Tian M, Cyrus J, Galimberti F, Memoli V, Buset AM, et al. Bexarotene plus erlotinib suppresses lung carcinogenesis independently of KRAS mutations in two clinical trials and transgenic models. Cancer Prev Res (Phila) In press, 2011.
12. Natale RB, Bodkin D, Govindan R, Aleckman BG, Rizvi NA, Capó A, et al. Vandetanib versus gefitinib in patients with advanced non–small-cell lung cancer: results from a two-part, double-blind, randomized phase II study. J Clin Oncol 2009;27:2523–9
13. Lara PN, Redman MW, Kelly K, Edelman MJ, Williamson SK, Crowley JJ, et al. Disease control rate at 8 wk predicts clinical benefit in advanced non-small-cell lung cancer: results from Southwest Oncology Group randomized trials. J Clin Oncol 2009;26:463–7.
14. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354–62.
15. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al: EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
16. Tsao MS, Sakurada A, Cutz JC, Zhu CQ, Kamel-Reid S, Squire J, et al. Erlotinib in lung cancer: molecular and clinical predictors of outcome. N Engl J Med 2005;353:133–44.
17. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
18. Zheng Z, Chen T, Li X, Haura E, Sharma A, Bepler G, et al. DNA synthesis and repair genes *RRM1* and *ERCC1* in lung cancer. N Engl J Med 2007;356:800–8.
19. Reynolds C, Obasaju C, Schell MJ, Li X, Zheng Z, Boulware D, et al. Randomized phase III trial of gemcitabine-based chemotherapy with in situ RRM1 and ERCC1 protein levels for response prediction in non-small cell lung cancer. J Clin Oncol 2009;34:5808–15.
20. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247–53.
21. Simon G, Sharma A, Li X, Hazelton T, Welsh F, Williams C, et al. Feasibility and efficacy of molecular analysis-directed individualized therapy in advanced non-small-cell lung cancer. J Clin Oncol 2007;19:2741–6.
22. Lee JJ, Gu X, Liu S. Bayesian adaptive randomization designs for targeted agent development. Clin Trials 2010;7:584–96.
23. Turke AB, Zejnullahu K, Wu YL, Song Y, Dias-Santagata D, Lifshits E, et al. Preexistence and clonal selection of MET amplification in EGFR mutant NSCLC. Cancer Cell 2010;17:77–88.
24. Cappuzzo F, Hirsch FR, Rossi E, Bartolini S, Ceresoli GL, Bemis L, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J Natl Cancer Inst 2005;97:643–55.
25. Edelman MJ, Smith R, Hausner P, Doyle LA, Kalra K, Kendall J, et al. Phase II trial of the novel retinoid, bexarotene, and gemcitabine plus carboplatin in advanced non-small cell lung cancer. J Clin Oncol 2005;24:5774–8.
26. Hirsch FR, Dziadziuszko R, Thatcher N, Mann H, Watkins C, Parums DV, et al. Epidermal growth factor receptor immunohistochemistry: comparison of antibodies and cutoff points to predict benefit from gefitinib in a phase 3 placebo-controlled study in advanced non small-cell lung cancer. Cancer 2008;112:1114–21.
27. Uzawa N, Sonoda I, Myo K, Takahashi K, Miyamoto R, Amagasa T. Fluorescence in situ hybridization for detecting genomic alterations of cyclin D1 and p16 in oral squamous cell carcinomas. Cancer 2007;110:2230–9.
28 Zhou X, Liu S, Kim ES. Bayesian adaptive design for targeted therapy development in lung cancer—a step toward personalized medicine. Clin Trials 2008;5:181–93.
29. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubenstein L, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.

Published OnlineFirst April 3, 2011; DOI: 10.1158/2159-8274.CD-10-0010



The BATTLE Trial: Personalizing Therapy for Lung Cancer

Edward S. Kim, Roy S. Herbst, Ignacio I. Wistuba, et al.

Cancer Discovery 2011;1:44-53. Published OnlineFirst April 3, 2011.