The BATTLE-2 Study: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer


See accompanying editorial on page 3595

ABSTRACT

Purpose

By applying the principles of real-time biopsy, biomarker-based, adaptively randomized studies in non–small-cell lung cancer (NSCLC) established by the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, we conducted BATTLE-2 (BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer), an umbrella study to evaluate the effects of targeted therapies focusing on KRAS-mutated cancers.

Patients and Methods

Patients with advanced NSCLC (excluding sensitizing EGFR mutations and ALK gene fusions) refractory to more than one prior therapy were randomly assigned, stratified by KRAS status, to four arms: (1) erlotinib, (2) erlotinib plus MK-2206, (3) MK-2206 plus AZD6244, or (4) sorafenib. Tumor gene expression profiling—targeted next-generation sequencing was performed to evaluate predictive and prognostic biomarkers.

Results

Two hundred patients, 27% with KRAS-mutated (KRAS mut+) tumors, were adaptively randomly assigned to erlotinib (n = 22), erlotinib plus MK-2206 (n = 42), MK-2206 plus AZD6244 (n = 75), or sorafenib (n = 61). In all, 186 patients were evaluable, and the primary end point of an 8-week disease control rate (DCR) was 48% (arm 1, 32%; arm 2, 50%; arm 3, 53%; and arm 4, 46%). For KRAS mut+ patients, DCR was 20%, 25%, 62%, and 44% whereas for KRAS wild-type patients, DCR was 36%, 57%, 49%, and 47% for arms 1, 2, 3, and 4, respectively. Median progression-free survival was 2.0 months, not different by KRAS status, 1.8 months for arm 1, and 2.5 months for arms 2 versus arms 3 and 4 in KRAS mut+ patients (P = .04). Median overall survival was 6.5 months, 9.0 and 5.1 months for arms 1 and 2 versus arms 3 and 4 in KRAS wild-type patients (P = .03). Median overall survival was 7.5 months in mesenchymal versus 5 months in epithelial tumors (P = .02).

Conclusion

Despite improved progression-free survival on therapy that did not contain erlotinib for KRAS mut+ patients and improved prognosis for mesenchymal tumors, better biomarker-driven treatment strategies are still needed.
lung cancer\(^4\) and has generated the impetus for using genotyping as a guide for clinical care of patients with lung cancer and for creating novel design paradigms in genomics-driven clinical trials.

In the 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) previously reported\(^6,7\) by our group, we prospectively biopsied tumors and, on the basis of tumor markers, we used adaptive randomization to assign patients with NSCLC to the treatment with the greatest potential benefit on the basis of cumulative data. The trial established the feasibility of performing core biopsies in pretreated patients with advanced disease and of using real-time biomarker analysis for treatment assignments\(^8\) and it represented a major step toward personalizing therapy for patients with NSCLC.

On this basis, the BATTLE-2 trial (BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer) capitalized on activity observed with sorafenib\(^9-11\) on enhanced Treated Patients With Advanced Non-Small Cell Lung Cancer) personalizing medicine (ClinicalTrials.gov numbers NCT00409968, NCT00411671, NCT00411632, NCT00410059, and NCT00410189) previously reported\(^6,7\) by our group, we prospectively biopsied tumors and, on the basis of tumor markers, we used adaptive randomization to assign patients with NSCLC to the treatment with the greatest potential benefit on the basis of cumulative data. The trial established the feasibility of performing core biopsies in pretreated patients with advanced disease and of using real-time biomarker analysis for treatment assignments\(^8\) and it represented a major step toward personalizing therapy for patients with NSCLC.

PATIENTS AND METHODS

**Patient Population**

Patients with pretreated NSCLC at the University of Texas MD Anderson Cancer Center and Yale Cancer Center who agreed to a baseline tumor biopsy, who had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, and who had multiple prior lines of therapy and stable or treated brain metastases were enrolled (details for eligibility are provided in the Data Supplement). Patients were excluded if their tumor harbored \(EGFR\) sensitizing mutations or \(ALK\) gene fusions, and they were erlotinib or crizotinib naïve. All participants provided written informed consent. The MD Anderson Cancer Center and Yale Cancer Center Institutional Review Boards approved the study. The trial was monitored by an independent data and safety monitoring board.

**Study Design**

BATTLE-2 was a randomized, phase II, multicenter, open-label study in patients with advanced NSCLC refractory to prior platinum-based chemotherapy (Fig 1). After molecular tumor biomarker assessments, patients were adaptively randomly assigned to four arms: arm 1, erlotinib 150 mg once per day (OSI Pharmaceuticals, Farmingdale, NY; Genentech, San Francisco, CA); arm 2, erlotinib 150 mg once per day and the AKT inhibitor MK-2206 135 mg once per week (Merck, Kenilworth, NJ); arm 3, MEK inhibitor AZD6244 100 mg per day (AstraZeneca, Wilmington, DE) and AKT inhibitor MK-2206 100 mg once per week; and arm 4, sorafenib 400 mg orally twice per day (Bayer, Whippany, NJ). Patients who received prior erlotinib were randomly assigned to one of arms 2, 3, or 4. Tumor evaluation studies were performed after two cycles (one cycle is 28 days) and every two cycles thereafter. \(KRAS\) mutation status was a stratification factor. All patients who received at least one cycle of treatment (4 weeks) were considered evaluable for response assessment, and all patients who were randomly assigned were evaluable for safety and survival analyses.

**Biopsy, Molecular Analysis, and Biomarker Profiling**

Patients had a mandatory baseline tumor tissue biopsy for biomarker analysis. Written informed consent was obtained from patients before the biopsy, which was performed under computed tomographic or spongographic guidance as previously described,\(^6,7\) including management of pneumothorax after the biopsy. Four to five fresh core needle biopsy tumor specimens approximately 1.5 cm long were collected, two of which were formalin-fixed immediately, paraffin embedded, and reviewed for presence, quantity, quality, and histologic type of tumor tissue by the dedicated pathologist. \(EGFR\) and \(KRAS\) Sanger sequencing (Data Supplement) and \(ALK\) fluorescence in situ hybridization testing\(^7\) were performed in Clinical Laboratory Improvement Amendments–certified laboratories within 2 weeks. The remaining three core needle biopsies were frozen, stored, and allocated for gene expression analysis by messenger RNA GeneChip Human Gene 1.0 ST Array from Affymetrix (Santa Clara, CA), which tested prospectively predefined signatures, including the epithelial mesenchymal transition (EMT) signature, and DNA-targeted next-generation sequencing (NGS; Foundation Medicine, Cambridge, MA) analysis\(^8\) in 140 tumors with sufficient material. Detailed methods are included in the Data Supplement.

**Statistical Analysis**

The accrual goal of stage 1 of the BATTLE-2 trial was 200 randomly assigned patients, which would allow at least 80% power with a 10% type I error rate to identify effective treatments for arms 2, 3, and 4 compared with arm 1. The overall power is 97.8% with a 20% family-wise type I error, which was chosen to prevent missing any potentially effective treatments; there was a plan to confirm the results in stage 2 and in future studies.\(^9\)

The primary end point was the 8-week disease control rate (DCR; complete or partial response or stable disease via Response Evaluation
Criteria in Solid Tumors [RECIST]). A Bayesian logistic regression model was applied to model the 8-week disease control status. Under the null hypothesis, we assumed that the 8-week DCRs were 0.3 for KRAS-wild-type (wt) and 0.1 for KRAS-mutant patients. Under the alternative hypothesis, and presuming one predictive marker per arm, we assumed that the 8-week DCR increased to 80% in the predictive marker–positive patients and remained at 30% in the predictive marker–negative patients. Equal randomization was performed in the first 70 patients. Subsequently, outcome adaptive randomization was used to incorporate the 8-week disease control status, KRAS mutation, and treatment into the calculation of the posterior probability of efficacy for treatments to allow more patients to be assigned to effective therapies and fewer patients to be assigned to less effective therapies. The posterior probability was continuously updated as the data became available. This learn-as-we-go approach leveraged accumulating data to improve outcome and is described in more detail elsewhere. Other end data became available. This learn-as-we-go approach leveraged accumulating

Standard statistical methods included Fisher’s exact test for contingency tables and Kaplan-Meier plots and log-rank test for univariable survival data. We used a logistic regression model in a multivariable analysis to assess the relationship of DCR with clinical factors and a Cox regression to model PFS and OS and interactions between KRAS mutation and erlotinib-containing therapy. SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.2.2 (Foundation for Statistical Computing, Vienna, Austria) were used.

### RESULTS

#### Patient Characteristics

A total of 334 patients provided consent, 60 were never biopsied because they did not fulfill eligibility criteria (n = 49) or had declining overall condition (n = 4) or decided to pursue alternative therapy (n = 7). Of 274 patients biopsied, 66 were not randomly assigned because they no longer fulfilled eligibility criteria (n = 34), they experienced a decline in overall condition (n = 17), they had a tumor that harbored a sensitizing EGFR mutation or an ALK gene fusion (n = 9), or they withdrew consent (n = 6). Randomly assigned and treated patients per treatment arm were 22 (erlotinib), 42 (erlotinib and MK-2206), 75 (MK-2206 plus AZD6244), and 61 (sorafenib; Fig 2). Eight randomly assigned patients never received therapy because they withheld consent (n = 5), had declining condition (n = 2), or had other reasons (n = 1).

Table 1 lists the distribution of the following patient characteristics: median age, 61 years (range, 26 to 82 years); female sex, 53%; ECOG PS of 0 to 1, 85%; never smoker, 22%; former smoker, 63%; current smoker, 16%; adenocarcinoma, 73.5%; and squamous cell carcinoma, 17.5%. KRAS mutations were present in 54 patients (27%); 75 patients (38%) had prior EGFR tyrosine kinase inhibitor treatment and a median of three prior therapies, with more patients heavily pretreated in arms 2, 3, and 4 (P = .03).

#### Efficacy

The overall 8-week DCR in 186 patients eligible for this analysis was 48% (Table 2), median PFS was 2.0 months (95% CI, 1.9 to 2.8 months), median OS was 6.5 months (95% CI, 5.1 to 7.6 months), and 1-year survival was 28%. Median follow-up was 20 months for PFS and 21 months for OS. There were no complete responses and only six partial responses in these heavily pretreated patients, three in arm 3 and three in arm 4. The overall 8-week DCRs were 32% (arm 1), 50% (arm 2), 53% (arm 3), and 46% (arm 4; pairwise Fisher’s exact test compared with arm 1 P = .26, .12, and .30, respectively; Table 2). Only PS was associated with improved DCR; the 8-week DCR for PS 0 was 77% versus only 47% for PS 1 and 36% for PS 2.

![Fig 2. CONSORT flow diagram of patient population and treatment assignments.](https://example.com/fig2.png)
Fisher’s exact test \( P = .03; \) Data Supplement), a significant association even after adjusting for other parameters in a logistic model (Data Supplement).

PFS was almost identical among all four arms (1.8, 2.5, 2.2, and 2.1 months for arms 1, 2, 3, and 4, respectively; Fig 3A). OS was not significantly different among the four arms (median, 7.6, 8.2,
Fig 3. (A) Progression-free survival (PFS) by treatment ($P = .17$), (B) overall survival (OS) by treatment ($P = .46$), (C) PFS of patients with KRAS wild-type (wt) tumors by treatment ($P = .13$), and hazard ratio (HR) for erlotinib-containing treatments versus treatments not containing erlotinib (HR, 0.76; 95% CI, 0.54 to 1.09). (D) PFS of patients with KRAS-mutated (KRAS mut+) tumors by treatment (HR, 1.95; 95% CI, 1.00 to 3.77; $P = .04$), (E) OS of patients with KRAS wt tumors by treatment (HR, 0.66; 95% CI, 0.45 to 0.97; $P = .03$), and (F) OS of patients with KRAS mut+ tumors by treatment (HR, 1.26; 95% CI, 0.65 to 2.46; $P = .50$). All $P$ values were based on two-sided log-rank test.
Biomarkers and Outcomes

Of the 54 KRAS mut+ patients, 52 were evaluable for the prespecified 8-week DCR assessment. There was no significant association between 8-week DCR and KRAS mutation status (Data Supplement).

PFS and OS were not different for patients with KRAS mut+ versus KRAS wt tumors for the whole study (Data Supplement). In KRAS wt patients, there was no difference in PFS between therapy containing erlotinib or not containing erlotinib (hazard ratio [HR] for erlotinib-containing treatments v not containing erlotinib 0.76; 95% CI, 0.54 to 1.09; P = .13; Fig 3C). Patients with KRAS mut+ tumors experienced a statistically significantly longer PFS if treated with therapy that did not contain erlotinib (HR, 1.95; 95% CI, 1.00 to 3.77; P = .04; Fig 3D). There is a significant qualitative interaction between KRAS mutation and erlotinib-containing therapy (P = .01). Patients with KRAS wt tumors treated with erlotinib-containing therapy had significantly better OS compared with those treated with therapy that did not contain erlotinib (HR, 0.66; 95% CI, 0.45 to 0.97; P = .03; Fig 3E), yet no difference in OS was seen among KRAS mut+ patients between these two treatment groups (HR, 0.26; 95% CI, 0.65 to 2.46; P = .50; Fig 3F), and the influence of the interaction between KRAS mutation and erlotinib-containing therapy on OS was not significant (P = .09). In arm 1, patients with KRAS mut+ tumors had a statistically significantly worse OS than those with KRAS wt tumors (median, 5.5 v 11.1 months; P = .02), but no significant differences were observed for KRAS mut+ compared with KRAS wt tumor-bearing patients in all other arms.

In tumors of 141 randomly assigned patients with adequate material for testing, we examined gene signatures described in the BATTLE study, including a sorafenib sensitivity signature generated from NSCLC cell lines and patient tumor biopsies22 that was not predictive of outcome in this set of patients, as well as an EMT signature23 that was associated with resistance to EGFR-generating treatments and/or delays were necessary in 18%, 43%, 39%, and 41% in arms 1, 2, 3, and 4, respectively. Nineteen patients (6.9%) experienced biopsy-related pneumothorax, and only two patients (0.7%) required hospitalization for management.

Toxicity

Toxicity, especially for the novel arms 2 and 3, was as expected on the basis of prior reports16,25 (Table 3). Average treatment compliance was more than 95% in all arms. There was only one grade 5 event observed in the sorafenib arm: esophageal hemorrhage with a centrally located tumor invading the esophagus and death possibly related to treatment. The most common grade 3 to 4 toxicity in arm 2 was diarrhea (16.7%); in arm 3, maculopapular rash (9.3%), and arm 4 (sorafenib), fatigue (13.1%). Treatment discontinuation rate was 9%, 14%, 13%, and 15% and dose reductions and/or delays were necessary in 18%, 43%, 39%, and 41% in arms 1, 2, 3, and 4, respectively. Nineteen patients (6.9%) experienced biopsy-related pneumothorax, and only two patients (0.7%) required hospitalization for management.

The phase II randomized BATTLE-2 trial confirmed the feasibility of biopsy-mandated, biomarker-based, adaptively randomized clinical study design in patients with pretreated advanced NSCLC. The trial data demonstrated the following key points: there was no significant association between 8-week DCR and KRAS mutation status; patients with KRAS wt tumors treated with erlotinib-containing therapy had better OS compared with those treated with therapy that did not contain erlotinib, whereas patients with KRAS mut+ tumors experienced longer PFS if treated with therapy that did not contain erlotinib and better 8-week DCR with MEK and AKT inhibitor therapy; and mesenchymal gene signature was associated with improved OS.

In all, 334 screened patients were needed to randomly assign 200 patients who reflected the heavily pretreated population with significant comorbid disease and declining PS, also underlying the rate of 3.2% partially because of a lack of validated predictive markers. The 8-week DCR observed in BATTLE-2 (48%) is similar to that observed in BATTLE-11 (46%) despite the exclusion of erlotinib-naïve patients with EGFR-sensitizing mutations (15% of BATTLE-1 patients).

In BATTLE-2, we prespecified an extremely limited set of markers, and our intent was to use the first half of the study (200 patients) to conduct prospective testing of biomarkers and/or gene signatures. Predictive markers were to be used to guide patient assignments in the second half of the study. Although the design theoretically provided advantages because clear predictive markers did not exist for any of the treatment arms, activity was modest yielding no new predictive markers and not warranting further exploration.

However, several interesting observations were derived from the trial. The EMT signature23 was not predictive of DCR or PFS in the overall group, but patients with mesenchymal tumors treated with MK-2206 and AZD6244 had improved PFS and those with mesenchymal tumors had improved OS compared with patients

6.4, and 5.5 months for arms 1, 2, 3, and 4, respectively; log-rank test P = .46; Fig 3B). In a multivariable Cox model, none of the parameters were significantly associated with PFS, and the only parameter associated with OS was PS (Data Supplement).
Fig 4. (A) The epithelial mesenchymal transition gene expression signature classifies BATTLE-2 tumors (all treatment arms) into epithelial (E) and mesenchymal (M). Distribution of KRAS-mutated tumors is shown. (B) Progression-free survival among epithelial and mesenchymal tumors (log-rank test $P = .12$). (C) Overall survival was superior for patients with mesenchymal tumors (log-rank test $P = .02$).
with epithelial tumors, an effect mostly driven by treatment with sorafenib. In a recent pan-cancer EMT analysis, there was a trend toward greater sensitivity of mesenchymal cell lines to sorafenib and to drugs that target PDGFR (overexpressed in mesenchymal tumors), consistent with the finding in this study. A major focus of BATTLE-2 was exploration of the efficacy of combined AKT and MEK inhibition for KRAS mut+ tumors. RAS signaling is activated through growth factor receptors or somatic mutations seen in 25% of lung adenocarcinomas, frequently in the context of other co-mutations. RAS has been an elusive target for direct targeting. Co-targeting of the Ras/Raf/MEK/ERK and PI3K/AKT parallel pathways on the basis of multiple points of cross-talk and negative feedback interactions can blunt compensatory pathway activation leading to antitumor effects. Indeed, in a KRAS-mutant lung cancer mouse model, combined MEK and PI3K/mammalian target of rapamycin target of rapamycin inhibition resulted in synergistic effects and tumor regression. In this trial, we used two potent selective inhibitors, MK-2206, an AKT inhibitor, and AZD6244, a non-ATP competitive inhibitor of MEK, a combination evaluated in a phase I study, which was partially run in parallel with our study with encouraging results (23% response rate in KRAS mut+ NSCLC). There were only three partial responses: two had available genomic data and one harbored both a KRAS G12C and an ARAF mutation suggesting multiple inputs in the MAPK signaling pathway and possibly conferring increased sensitivity to MEK inhibition. The observed heterogeneity of response among patients with KRAS-mut+ cancers likely results from biologically distinct subgroups with different therapeutic vulnerabilities. Our experience mirrors that of several other trials evaluating combinations of PI3K/AKT and MEK inhibitors that have
demonstrated modest activity and poor tolerance to combinations related to on-target inhibition of the MAPK and PI3K pathways in normal tissues.

Complex mutational background tumors encountered in heavily pretreated patients may be better addressed with novel immunotherapy agents \(^{39,40}\) or other combinations of targeted therapy with or without immunotherapy.

The BATTLE-2 study showed the utility of real-time biopsies for broad profiling of tumors that serve as a discovery vehicle for better target selection. We are currently pursuing alternative strategies in targeting KRAS mut+ tumors by incorporating knowledge derived from BATTLE-2.

### Authors’ Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at www.jco.org.

### References


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