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ORIGINAL REPORT

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

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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.

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INTRODUCTION

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer-related death and accounts for more than a million deaths per year worldwide.[1] The disease is usually diagnosed at later stages, when curative treatment is not available.[2] The benefit from platinum-based doublet chemotherapy is modest.[3] Lung cancers are biologically and molecularly diverse[4] and have various responses to both traditional chemotherapy and targeted therapy designed to address molecular alterations that drive cancer progression.[5] The rapid evolution of genomic profiling has dramatically accelerated our knowledge of the diversity of 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 understanding of lung cancer biology, and on the availability of several promising agents, including MK-2206, an allosteric AKT inhibitor,[12] and AZD6244, an MEK inhibitor.[13] We could thus test novel hypotheses derived from a *KRAS*-mutant lung cancer mouse model in which combined MEK and PI3K/mammalian target of rapamycin inhibition resulted in synergistic tumor regression[14] and also test preclinical information that justified combining erlotinib and MK-2206[15,16] as a means of overcoming resistance to EGFR inhibitors conferred by continued PI3K pathway activation and hepatocyte growth factor. The goals of the trial were to evaluate efficacy and identify predictive biomarkers for targeted therapies in the first stage, aiming at optimized patient selection for these therapies in the second stage. BATTLE-2 was designed with a particular emphasis on targeting mutant Kirsten rat sarcoma viral oncogene homolog (*KRAS* mut+) NSCLC refractory to platinum-based regimens. Here we report the results of the first stage of the BATTLE-2 trial.

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 sonographic guidance as previously described,[6,8] 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[17] 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[18] 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.[19]

The primary end point was the 8-week disease control rate (DCR; complete or partial response or stable disease via Response Evaluation

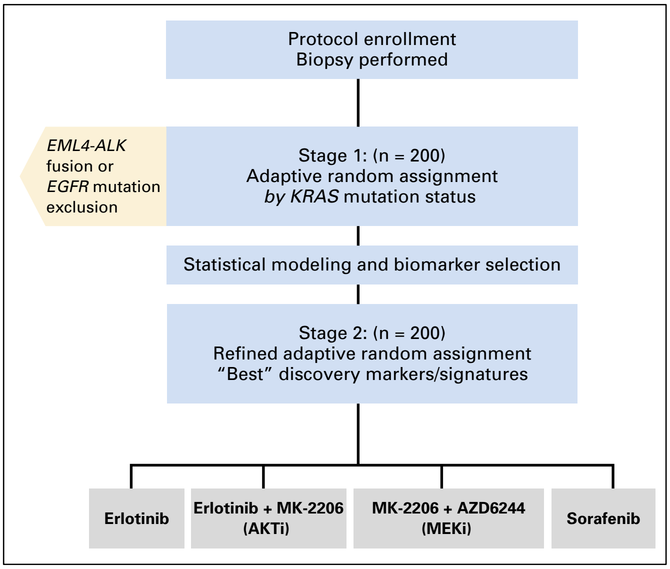


Fig 1. BATTLE-2 trial schema. AKTi, AKT inhibitor; MEKi, MEK inhibitor.

Criteria in Solid Tumors [RECIST]),[20] a previously validated end point.[6,21] 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.[19] Other end points included response rate, progression-free survival (PFS), overall survival (OS), and toxicity. Planned exploratory objectives were each treatment's efficacy in relation to biomarker profiles. PFS and OS were assessed from the date of drug start to the earliest sign of disease progression (PFS) or death as a result of any cause (PFS and OS). 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. 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 withdrew 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

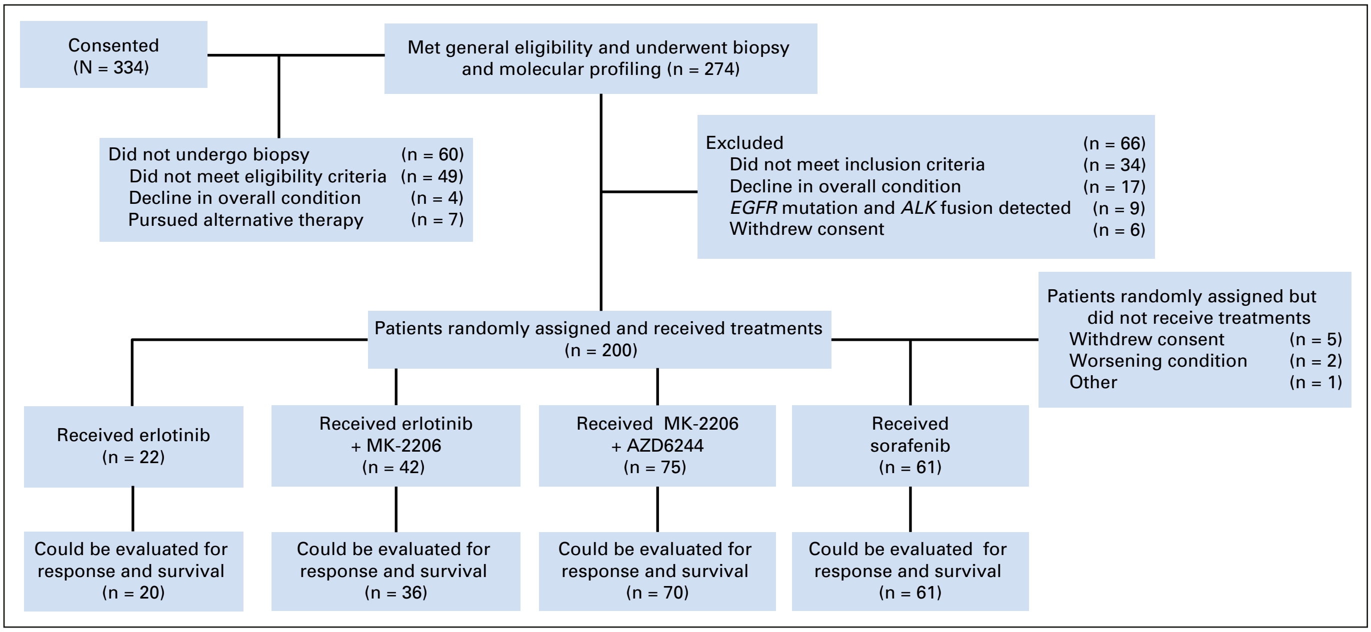


Fig 2. CONSORT flow diagram of patient population and treatment assignments.

Table 1. Summary of Patient Characteristics

Characteristic	Arm 1 (erlotinib)		Arm 2 (erlotinib + MK-2206)		Arm 3 (MK-2206 + AZD6244)		Arm 4 (sorafenib)		Total		
	No.	%	No.	%	No.	%	No.	%	No.	%	*P* *
Age, years											
≤ 49	2	9.1	2	4.8	6	8.0	7	11.5	17	8.5	.72
50-59	8	36.4	16	38.1	27	36.0	19	31.1	70	35.0	
60-69	10	45.5	12	28.6	29	38.7	24	39.3	75	37.5	
70+	2	9.0	12	28.6	13	17.3	11	18.0	38	19.0	
Median (range)	61 (34-82)		62 (43-78)		61 (26-76)		62 (35-79)		61 (26-82)		.94†
Sex											
Female	10	45.5	15	35.7	49	65.3	32	52.5	106	53.0	.02
Male	12	54.5	27	64.3	26	34.7	29	47.5	94	47.0	
Race/ethnicity											
White	18	81.8	40	95.2	67	89.3	51	83.6	176	88.0	.23
Other	4	18.2	2	4.8	8	10.7	10	16.4	24	12.0	
Smoking status											
Never	3	13.6	8	19.0	19	25.3	13	21.3	43	21.5	.50
Former	17	77.3	26	61.9	48	64.0	35	57.4	126	63.0	
Current	2	9.1	8	19.0	8	10.7	13	21.3	31	15.5	
KRAS mut+											
No	16	72.7	34	81.0	53	70.7	43	70.5	146	73.0	.63
Yes	6	27.3	8	19.0	22	29.3	18	29.5	54	27.0	
Prior erlotinib therapy											
No	22	100	27	64.3	42	56.0	34	55.7	125	62.5	< .001
Yes			15	35.7	33	44.0	27	44.3	75	37.5	
ECOG PS											
0	3	13.6	4	9.5	6	8.0	4	6.6	17	8.5	.59
1	17	77.3	31	73.8	61	81.3	44	72.1	153	76.5	
2	2	9.1	7	16.7	8	10.7	13	21.3	30	15.0	
No. of prior therapies											
1	8	36.4	4	9.5	11	14.7	6	9.8	29	14.5	.14
2	6	27.3	12	28.6	13	17.3	17	27.9	48	24.0	
3	4	18.2	7	16.7	21	28.0	15	24.6	47	23.5	
4	3	13.6	9	21.4	16	21.3	13	21.3	41	20.5	
5			7	16.7	6	8.0	3	4.9	16	8.0	
≥ 6	1	4.5	3	7.1	8	10.7	7	11.5	19	9.5	
Median (range)	2.0 (1.0-6.0)		3.0 (1.0-7.0)		3.0 (1.0-10.0)		3.0 (1.0-9.0)		3.0 (1.0-10.0)		.03†
Histology											
Adenocarcinoma	14	63.6	27	64.3	63	84.0	43	70.5	147	73.5	.05
Squamous cell	7	31.8	11	26.2	8	10.7	9	14.8	35	17.5	
Other	1	4.5	4	9.5	4	5.3	9	14.8	18	9.0	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS* mut+, *KRAS* mutation.
*Fisher's exact test.
†Kruskal-Wallis test.

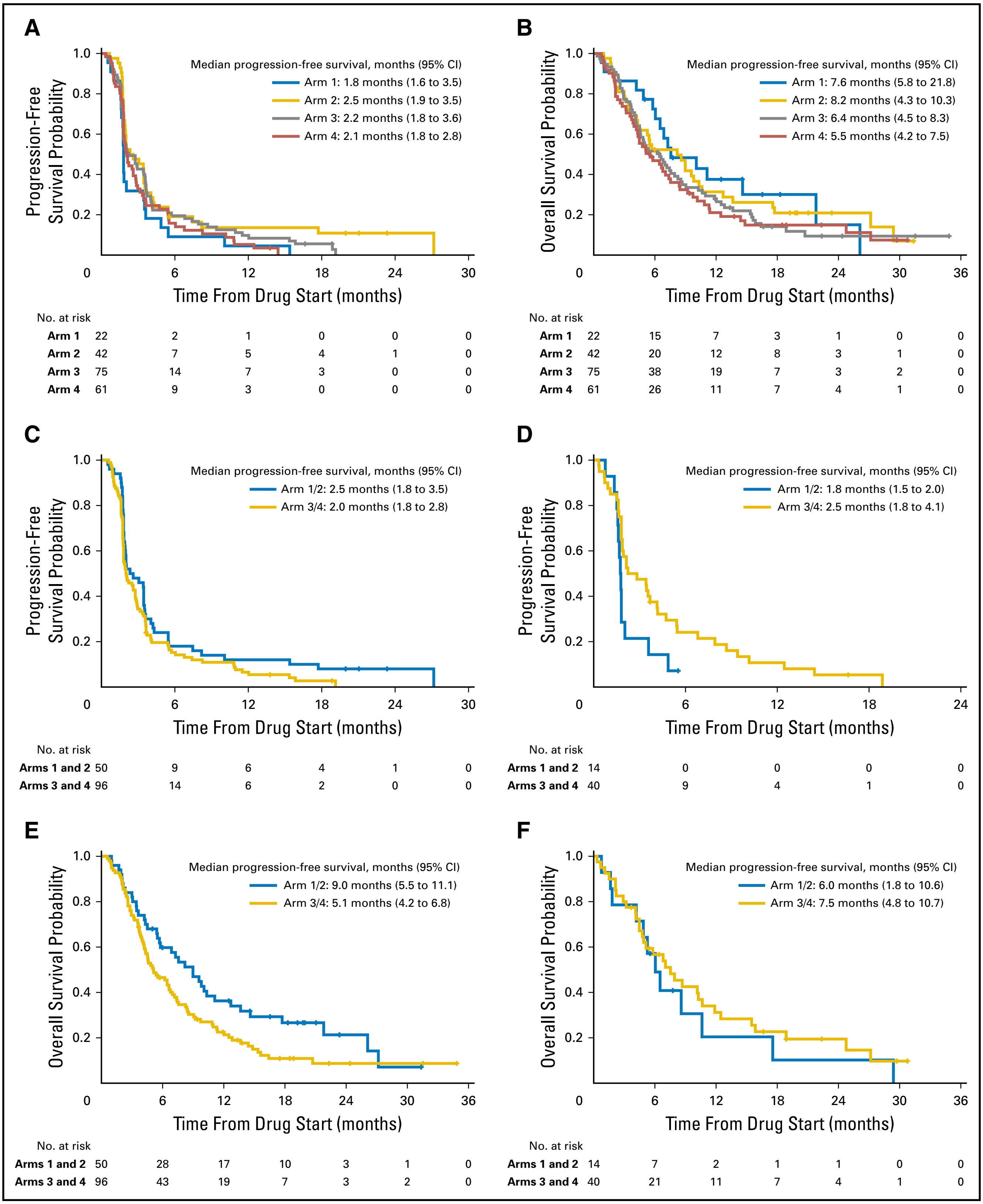
(Fisher's exact test *P* = .03; Data Supplement), a significant association even after adjusting for other parameters in a logistic model (Data Supplement).

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,

Table 2. Summary of 8-Week Response by Treatment

Response	Arm 1 (erlotinib)		Arm 2 (erlotinib + MK-2206)		Arm 3 (MK-2206 + AZD6244)		Arm 4 (sorafenib)		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
PR	0	0	0	0	3	4	3	5	6	3
SD	6	32	18	50	34	49	25	41	83	45
8-week DCR (PR + SD)	6	32	18	50	37	53	28	46	89	48
PD	13	68	18	50	33	47	33	54	97	52
Not evaluable*	3		6		5		0		14	

Abbreviations: DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease
*Two patients were not evaluable because they did not complete treatment, one because the patient was retrospectively found to be noneligible because the tumor harbored an *EGFR*-sensitizing mutation that was not detected during screening.



No. at risk	0	6	12	18	24	30
Arm 1	22	2	1	0	0	0
Arm 2	42	7	5	4	1	0
Arm 3	75	14	7	3	0	0
Arm 4	61	9	3	0	0	0

No. at risk	0	6	12	18	24	30	36
Arm 1	22	15	7	3	1	0	0
Arm 2	42	20	12	8	3	1	0
Arm 3	75	38	19	7	3	2	0
Arm 4	61	26	11	7	4	1	0

No. at risk	0	6	12	18	24	30
Arms 1 and 2	50	9	6	4	1	0
Arms 3 and 4	96	14	6	2	0	0

No. at risk	0	6	12	18	24
Arms 1 and 2	14	0	0	0	0
Arms 3 and 4	40	9	4	1	0

No. at risk	0	6	12	18	24	30	36
Arms 1 and 2	50	28	17	10	3	1	0
Arms 3 and 4	96	43	19	7	3	2	0

No. at risk	0	6	12	18	24	30	36
Arms 1 and 2	14	7	2	1	1	0	0
Arms 3 and 4	40	21	11	7	4	1	0

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.

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).

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 biopsies[22] that was not predictive of outcome in this set of patients, as well as an EMT gene signature[23] that was associated with resistance in EGFR wt patients who received erlotinib. Patient tumors were scored to classify them as mesenchymal (EMT score > 0; $n = 68$) or epithelial (EMT score < 0; $n = 73$). There was no significant association between 8-week DCR and EMT score (Wilcoxon rank sum test $P = .72$; Data Supplement). EMT gene signature[23] analysis (Fig 4A) revealed that PFS was not different in epithelial versus mesenchymal tumors (Fig 4B), whereas analysis by arm revealed improved PFS for patients with mesenchymal tumors treated with the MEK inhibitor (arm 3; $P = .04$; Data Supplement). A statistically significantly improved OS was seen in patients with mesenchymal tumors (log-rank test $P = .02$; Fig 4C). The most pronounced effect was found for patients treated with sorafenib and among *KRAS* mut+ tumors (log-rank test $P = .01$; Data Supplement). Among rare responders, genomic profiling revealed an exon 19 deletion *EGFR* mutation on the erlotinib arm not detected at study entry (excluded from DCR analysis; Table 2), a *KRAS* G12C mutation, an *ARAF* mutation (R124H; predicted to be associated with sensitivity to MEK inhibition; first responder), an *FBXW7* mutation (R479Q), and a short variant of unknown significance in the *NOTCH1* gene both predicted to potentially contribute to sensitivity to AKT inhibition[24] (second responder) on arm 3 (MK-2206 and AZD6244).

Toxicity

Toxicity, especially for the novel arms 2 and 3, was as expected on the basis of prior reports[16,25] (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.

DISCUSSION

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 response 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-1[6] (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 signature,[23] 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

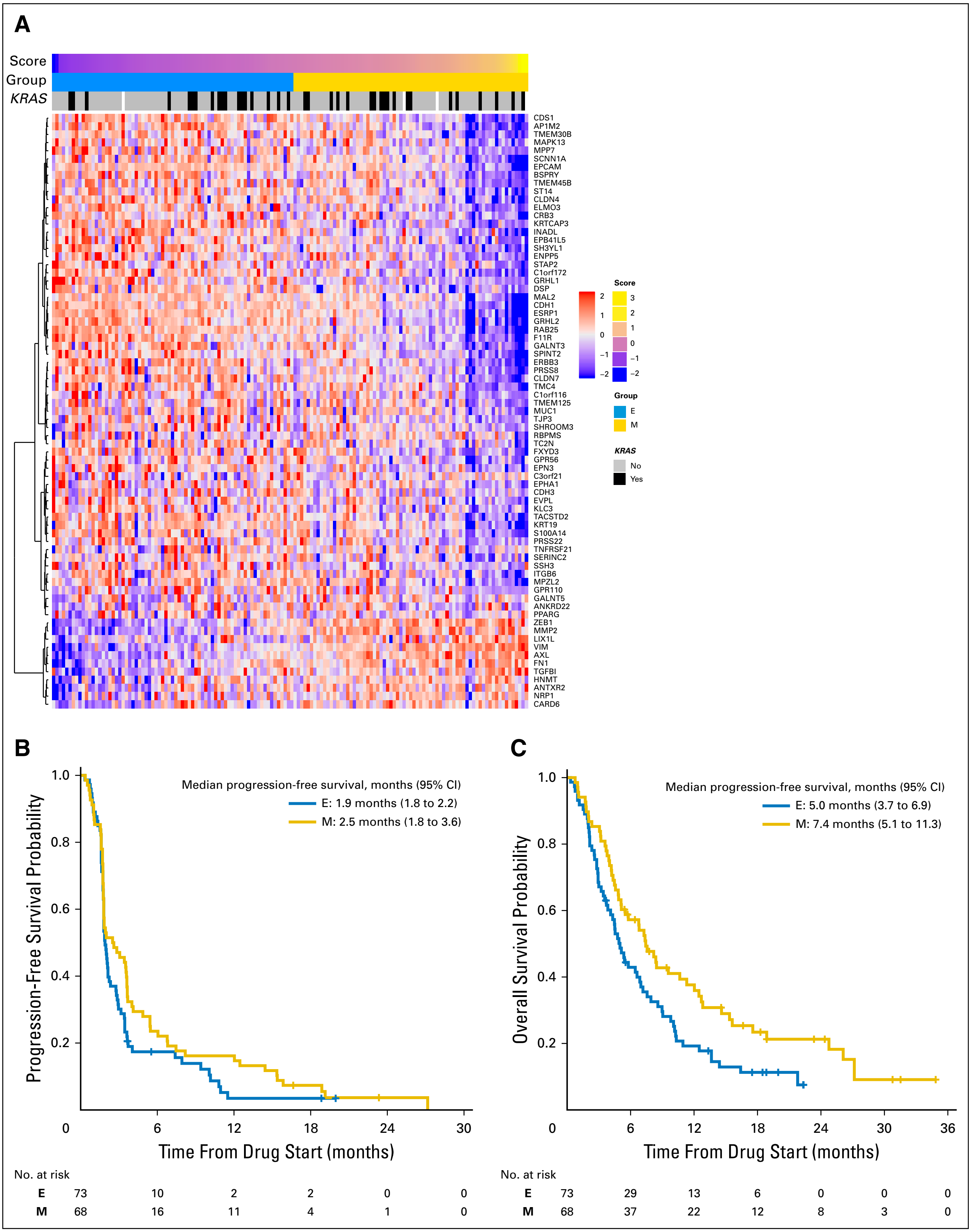


Fig 4. (A) The epithelial mesenchymal transition gene expression signature classifies BATTLE-2 tumors (all treatment arms) into epithelial (E) and mesenchymal (M). Distribution of *KRAS*-mutated tumors is shown. (B) Progression-free survival among epithelial and mesenchymal tumors (log-rank test *P* = .12). (C) Overall survival was superior for patients with mesenchymal tumors (log-rank test *P* = .02).

Table 3. Treatment-Related (including definite, possible, and probable) Adverse Events of All Grades and Grades 3 to 5 Occurring in More Than 10% of Patients in Any Arm

	Total (n = 200)				Arm 1 (n = 22)				Arm 2 (n = 42)				Arm 3 (n = 75)				Arm 4 (n = 61)			
	All Grades		Grades 3-5		All Grades		Grades 3-5		All Grades		Grades 3-5		All Grades		Grades 3-5		All Grades		Grades 3-5	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Fatigue	74	37.0	16	8.0	2	9.1	1	4.5	15	35.7	1	2.4	31	41.3	6	8.0	26	42.6	8	13.1
Diarrhea	73	36.5	13	6.5	8	36.4	2	9.1	24	57.1	7	16.7	26	34.7	2	2.7	15	24.6	2	3.3
Rash																				
Maculopapular	70	35.0	9	4.5	3	13.6	0	0.0	14	33.3	1	2.4	29	38.7	7	9.3	24	39.3	1	1.6
Acneiform	61	30.5	6	3.0	11	50.0	1	4.5	18	42.9	1	2.4	29	38.7	4	5.3	3	4.9	0	0.0
Nausea	57	28.5	5	2.5	7	31.8	1	4.5	13	31.0	2	4.8	25	33.3	1	1.3	12	19.7	1	1.6
Vomiting	56	28.0	5	2.5	5	22.7	0	0.0	10	23.8	3	7.1	27	36.0	2	2.7	14	23.0	0	0.0
Dry skin	50	25.0	4	2.0	7	31.8	0	0.0	12	28.6	0	0.0	13	17.3	3	4.0	18	29.5	1	1.6
Anorexia	46	23.0	1	0.5	6	27.3	0	0.0	16	38.1	0	0.0	9	12.0	0	0.0	15	24.6	1	1.6
Increased AST	46	23.0	5	2.5	5	22.7	0	0.0	5	11.9	0	0.0	29	38.7	5	6.7	7	11.5	0	0.0
Hyperglycemia	41	20.5	3	1.5	2	9.1	0	0.0	11	26.2	1	2.4	24	32.0	2	2.7	4	6.6	0	0.0
Oral mucositis	40	20.0	6	3.0	3	13.6	1	4.5	13	31.0	3	7.1	14	18.7	1	1.3	10	16.4	1	1.6
Increased alkaline phosphatase	39	19.5	2	1.0	2	9.1	0	0.0	10	23.8	0	0.0	17	22.7	1	1.3	10	16.4	1	1.6
Weight loss	38	19.0	1	0.5	3	13.6	0	0.0	11	26.2	0	0.0	2	2.7	0	0.0	22	36.1	1	1.6
Increased ALT	32	16.0	4	2.0	0	0.0	0	0.0	5	11.9	0	0.0	22	29.3	4	5.3	5	8.2	0	0.0
Pruritus	22	11.0	1	0.5	1	4.5	0	0.0	4	9.5	0	0.0	8	10.7	1	1.3	9	14.8	0	0.0
Other skin and subcutaneous tissue disorders, specify	19	9.5	0	0.0	3	13.6	0	0.0	3	7.1	0	0.0	8	10.7	0	0.0	5	8.2	0	0.0
Dyspnea	18	9.0	4	2.0	1	4.5	0	0.0	2	4.8	1	2.4	8	10.7	1	1.3	7	11.5	2	3.3
Palmar-plantar erythrodysesthesia syndrome	17	8.5	5	2.5	1	4.5	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0	15	24.6	5	8.2
Dry mouth	16	8.0	0	0.0	1	4.5	0	0.0	6	14.3	0	0.0	6	8.0	0	0.0	3	4.9	0	0.0
Increased blood bilirubin	13	6.5	1	0.5	5	22.7	0	0.0	2	4.8	0	0.0	1	1.3	0	0.0	5	8.2	1	1.6
Hyponatremia	13	6.5	3	1.5	1	4.5	0	0.0	3	7.1	1	2.4	0	0.0	0	0.0	9	14.8	2	3.3
Alopecia	13	6.5	0	0.0	0	0.0	0	0.0	1	2.4	0	0.0	5	6.7	0	0.0	7	11.5	0	0.0
Hypertension	13	6.5	3	1.5	0	0.0	0	0.0	1	2.4	0	0.0	2	2.7	0	0.0	10	16.4	3	4.9
Anemia	11	5.5	0	0.0	0	0.0	0	0.0	2	4.8	0	0.0	2	2.7	0	0.0	7	11.5	0	0.0
Hypoalbuminemia	10	5.0	0	0.0	1	4.5	0	0.0	1	2.4	0	0.0	1	1.3	0	0.0	7	11.5	0	0.0
Dysgeusia	9	4.5	0	0.0	1	4.5	0	0.0	5	11.9	0	0.0	3	4.0	0	0.0	0	0.0	0	0.0
Increased creatinine	9	4.5	0	0.0	0	0.0	0	0.0	5	11.9	0	0.0	2	2.7	0	0.0	2	3.3	0	0.0
Hoarseness	9	4.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0	8	13.1	0	0.0
Epistaxis	8	4.0	0	0.0	3	13.6	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0	4	6.6	0	0.0
Hypophosphatemia	8	4.0	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0	8	13.1	1	1.6

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.[26] Interestingly, this effect of EMT on OS (all arms, log-rank test $P = .02$) and among sorafenib-treated patients (log-rank test $P = .01$) was maintained among patients with *KRAS* mut+ tumors (Data Supplement). Sorafenib significantly reduces the epigenetic switching of critical EMT-associated genes by potentiating histone acetylation through regulation of expression of histone-modifying enzymes.[27] It can inhibit transforming growth factor β_1–induced EMT and hepatocyte growth factor–mediated EMT in hepatocytes,[28] the latter effect being mediated by inhibition of MAPK signaling, possibly implicated in the improved PFS observed for patients with mesenchymal tumors treated with AZD6244.[29]

A major focus of BATTLE-2 was exploration of the efficacy of combined AKT and MEK inhibition for *KRAS* mut+ patients. RAS signaling[30] 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.[31] 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[32] 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 inhibition resulted in synergistic effects and tumor regression.[14] In this trial, we used two potent selective inhibitors, MK-2206, an AKT inhibitor, and AZD6244, a non-ATP competitive inhibitor of MEK,[33] a combination evaluated in a phase I study,[34] 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 reflects the complex co-mutational landscape of *KRAS* mut+ tumors that defines biologically distinct subgroups with different therapeutic vulnerabilities.[35] Our experience mirrors that of several other trials evaluating combinations of PI3K/AKT and MEK inhibitors[25,36-38] 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.

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

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

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