# Monotherapy Administration of Sorafenib in Patients With Non–Small Cell Lung Cancer (MISSION) Trial

## *A Phase III, Multicenter, Placebo-Controlled Trial of Sorafenib in Patients with Relapsed or Refractory Predominantly Nonsquamous Non–Small-Cell Lung Cancer after 2 or 3 Previous Treatment Regimens*

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**Introduction:** Sorafenib monotherapy has shown benefits in phase II trials as third-/fourth-line treatment in patients with non–small-cell lung cancer (NSCLC).

**Methods:** The phase III, multinational, double-blind, placebo-controlled Monotherapy admInistration of Sorafenib in patientS wIth nOn–small-cell luNg cancer (MISSION) trial randomized patients with advanced relapsed/refractory NSCLC, following two or three prior treatment regimens, to sorafenib 400 mg twice a day (n = 350) or matching placebo (n = 353) plus best supportive care. The primary end point was overall survival (OS); secondary end points included progression-free survival (PFS) and time to progression. Epidermal growth factor receptor and KRAS mutation status was analyzed in archival tumor and/or circulating tumor DNA from blood samples obtained during screening.

**Results:** Median OS was similar in the sorafenib and placebo groups (8.2 versus 8.3 mo; hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.84–1.17; $p = 0.47$). Median PFS (2.8 versus 1.4 mo; HR, 0.61; 95% CI, 0.51–0.72; $p < 0.0001$), and time to progression (2.9 versus 1.4 mo; HR, 0.54; 95% CI, 0.45–0.65; $p < 0.0001$) were significantly greater with sorafenib than with placebo. Among the 89 patients with epidermal growth factor receptor mutations, OS (13.9 versus 6.5 mo; HR, 0.48; 95% CI, 0.30–0.76; $p = 0.002$) and PFS (2.7 versus 1.4 mo; HR, 0.27; 95% CI, 0.16–0.46; $p < 0.001$) were significantly higher with sorafenib than placebo. PFS was significantly longer with sorafenib than placebo in patients with either wild-type or mutated KRAS, but OS was similar. Common drug-related adverse events were rash/desquamation, diarrhea, and fatigue, consistent with the safety profile of sorafenib.

**Conclusions:** Third-/fourth-line sorafenib therapy did not significantly increase OS in patients with relapsed/refractory NSCLC, despite significantly increasing PFS.

**Key Words:** Non–small-cell lung cancer, Molecular targeted therapy, Sorafenib, KRAS mutation, EGFR mutation.

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Patients with non–small-cell lung cancer (NSCLC) who have relapsed or have failed to respond to more than two conventional chemotherapeutic regimens have very limited choices for further therapy.[1] Erlotinib, which targets the

epidermal growth factor receptor (EGFR), and crizotinib, which targets EML4/ALK, are the only agents currently approved for third-line therapy in the United States.[2] Both of these agents are also recommended for first-line therapy in patients with appropriate genomic alterations.[2] The efficacy of agents in earlier settings has allowed patients to survive long enough to benefit from treatment after two to three prior therapies, thus creating a need for additional active agents.

Sorafenib is an oral multikinase inhibitor targeting receptor tyrosine and serine/threonine kinases, including receptors for vascular endothelial growth factor (VEGF) and platelet-derived growth factor and c-Kit. This agent is approved for the treatment of patients with advanced renal cell and hepatocellular carcinoma.[3–5]

The clinical activity of sorafenib as therapy for previously treated patients with NSCLC was examined in two phase II trials.[6,7] In the first, a multicenter, uncontrolled trial of sorafenib monotherapy (400 mg twice a day) in 54 patients with relapsed or refractory NSCLC, most of whom had stage IV disease, the median overall survival (OS) for the evaluable population (n = 51) was 6.7 months, with a median progression-free survival (PFS) of 2.7 months. Although there were no confirmed responses and the primary end point was not met, stable disease (SD) was confirmed for 30 patients (58.5%), who had a median OS of 5.5 months and a median PFS of 3.4 months (range, 0.9–13.1 mo).[6]

The second phase II trial enrolled patients who failed at least two chemotherapy regimens and used a double-blinded, placebo-controlled, randomized discontinuation design.[7] In step 1, 342 patients received 2 months of open label treatment with sorafenib. Patients who had an objective tumor response (complete response or partial response [PR]) continued treatment with sorafenib and those who developed progressive disease discontinued treatment. Patients who had SD after step 1 (n = 107) were randomized in step 2 to receive sorafenib or placebo. At completion of step 2, 47% versus 19% had SD ($p = 0.01$). Median PFS was 3.6 for sorafenib versus 2 months for placebo, and median OS was 11.9 months for sorafenib versus 9 months for placebo. Trials have also assessed the efficacy of sorafenib in patients with NSCLC and KRAS mutations. For example, a preliminary trial in 10 NSCLC patients with KRAS mutations previously treated with 1–4 lines of chemotherapy found that three patients achieved PRs, three had minimal responses, three had SD, and one had an unknown response, making the disease control rate (DCR) rate 90%.[8] Moreover, the median PFS in these 10 patients was 3 months (95% confidence interval [CI], 2.2–3.8 mo). In an expanded phase II trial, 57 patients with KRAS mutations were treated with sorafenib; of these, five achieved PR and 25 SD, making the DCR rate 52.6%.[9] The median PFS was 2.3 months, and the median OS was 5.3 months. Taken together, these results suggest that sorafenib may be effective in NSCLC patients with KRAS mutations.

Further indication that sorafenib has clinical activity in advanced NSCLC comes from the recent results from the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial also indicated that sorafenib has clinical activity in patients with advanced NSCLC.[10] The patients in that trial randomized to sorafenib, based on biomarker profiles, had an overall DCR of 58%, ranging from 61% for patients with KRAS mutation-positive tumors and 64% for patients with EGFR wild-type tumors to 23% for patients with EGFR mutation-positive tumors.

The phase III Monotherapy admInistration of Sorafenib in patientS wIth nOn–small-cell luNg cancer (MISSION) trial was initiated to compare the efficacy and safety of third-/fourth-line monotherapy with sorafenib in combination with best supportive care (BSC) and with BSC alone for increasing OS in patients with predominantly nonsquamous NSCLC.

## METHODS AND PATIENTS

### Study Design

This trial was a phase III, randomized, double-blind, placebo-controlled trial conducted in 33 countries in Europe, North and South America, and Asia-Pacific. Patients were randomized 1:1 in a double-blind fashion to receive oral sorafenib (two tablets of 200 mg) plus BSC or matching placebo twice daily (morning and evening) plus BSC on a continuous basis, until disease progression based on unequivocal findings, intolerable toxicity, withdrawal of patient consent, or at the investigator's discretion. Because patients visited the clinic every 3 weeks, 21-day treatment cycles were tracked, with no scheduled interruptions of treatment between these cycles. Dose modifications were allowed to 400 mg/day and then to 400 mg every other day, as were dose delays, similar to those permitted in previous sorafenib trials, primarily for hand–foot skin reactions and hematologic toxicities.[5,11] Patients were assessed every 3 weeks, with tumor assessments performed every 6 weeks.

### Patients

Patients were included if they were greater than or equal to 18 years of age (≥20 years in Japan) and had cytologically or histologically confirmed diagnosis of advanced relapsed/refractory NSCLC following at least two but no more than three prior treatment regimens. All patients had measurable disease (≥20 mm in one dimension using conventional techniques) or nonmeasurable disease (<20 mm using conventional techniques or <10 mm using spiral computed tomography), with all sites evaluated within 4 weeks before first dose of study drug; an Eastern Cooperative Oncology Group performance score of 0 or 1; a life expectancy more than or equal to 12 weeks; and adequate bone marrow, liver, and renal function.

Patients were excluded if they had NSCLC of predominantly squamous-cell histology (because of safety issues with sorafenib in patients with squamous NSCLC[12]) or a previous or concurrent cancer at the primary site that was histologically distinct from NSCLC, except for cervical carcinoma in situ, treated basal cell carcinoma, or superficial bladder tumor. Patients were also excluded if they had a history of cardiac disease; a history of infection with HIV or evidence of chronic hepatitis B or C virus infection; a history of organ allograft; any active, clinically serious infection; bleeding diathesis or coagulopathy; renal dialysis; or hemorrhage/bleeding events. Patients were also excluded if they had been treated with any other VEGF receptor inhibitor, except for bevacizumab; if they had been treated with

an investigational drug or device within 4 weeks of study entry; or if they had received radiotherapy within 3 weeks or major surgery within 4 weeks of study entry. Patients were stratified by number of prior lines of treatment (2 versus 3), presence versus absence of brain metastases, prior treatment versus no prior treatment with an EGFR inhibitor, and geographic region (North America, Northern/Western, Europe and Australia versus South America, Eastern Europe and Asia-Pacific).

Patients were allowed to continue treatment with nonconventional therapies and vitamin/mineral supplements that, in the opinion of the investigator, did not interfere with the study endpoints. Patients were told to avoid chronic use of CYP3 inducers because of potential interactions with sorafenib. Patients using medications with narrow therapeutic indices (e.g., warfarin, digoxin, phenytoin, cyclosporine, and quinidine) were monitored proactively.

This trial was registered at www.clinicaltrials.gov as NCT00863746 and as EudraCT Number 2008-006914-62.

### Efficacy Assessments

The primary objective of this phase III study was OS, which was measured from the date of randomization until the date of death from any cause. Patients remaining alive at the end of the study were censored. The secondary efficacy objectives of this trial were PFS, calculated from the date of randomization until document disease progression or death; DCR; overall response rate (ORR); and time to progression (TTP), calculated from the date of randomization until documented disease progression. Treatment response was evaluated by the investigator using Response Evaluation Criteria In Solid Tumors (RECIST) tumor response criteria.[13] Although efforts were made to radiologically document disease progression using computed tomography or magnetic resonance imaging, the date of clinical disease progression was used throughout, with no independent review of radiologic images. Efficacy was similarly assessed in prospectively defined biomarker subgroups.

### Safety Assessments

Patients receiving at least one dose of study medication were included in the safety population. All adverse events were reported and graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0, except for hand–foot skin reaction, which was graded as described.[5,11] Patients were assessed for safety during clinic visits every 3 weeks.

### Mutation Analysis

Archival tumor samples and/or fresh blood samples obtained during screening were collected from randomized patients who consented to the biomarker analysis. EGFR and KRAS mutation status was analyzed in tumor samples and/or in circulating tumor DNA isolated from plasma using Beads, Emulsions, Amplification, and Magnetics; Inostics, Hamburg, Germany (BEAMing),[14,15] a method that has been utilized to detect EGFR mutations in serum and tissue samples from patients with lung adenocarcinomas.[16] The sensitivity of this assay was 0.02% for plasma and 1% for tumor tissue.

### Statistical Analyses

The sample size was determined according to calculations based on OS using EAST 5 software (Cytel Inc., Cambridge, MA). The study was designed to detect a 33% increase in median OS using a one-sided alpha of 0.025 with a power of 90%. A total of 520 events were required after a 1:1 randomization of patients to sorafenib and placebo.

Efficacy outcomes were analyzed for the intent-to-treat population, defined as all randomized subjects. OS was analyzed using stratified log rank tests and the same factors used during randomization. The null hypothesis, "the survival curves for sorafenib and placebo are identical at any time point," was tested against the alternative hypothesis, "the sorafenib curve is higher than the placebo time curve for at least one time point." The hazard ratio (HR) and 95% CI for OS were calculated using the Cox model stratified by the randomization factors. Separate Kaplan–Meier estimates for survival were determined for each study treatment. The secondary efficacy endpoints of PFS, DCR, ORR, and TTP were evaluated by each investigator using RECIST tumor response criteria[6] and analyzed using a one-sided significance level of 0.025. Safety was analyzed in all patients who received one dose or more of study drug. In the patients with biomarker samples available, an analysis for OS was performed where an interaction term for treatment and biomarker activity was additionally included into the Cox model.

## RESULTS

### Patient Disposition

A total of 703 patients were randomized to sorafenib (n = 350) and placebo (n = 353) (Fig. 1). Baseline demographic characteristics were similar for the two groups (Table 1).

Patients in the sorafenib group received a median of 12.0 weeks of treatment (mean, 18.0 weeks) compared with a median of 6.3 weeks for the placebo group (mean, 11.6 weeks). During sorafenib treatment, 181 patients (51.7%) had dose interruptions, including 167 for adverse events; 17 for subject error; and three each for site error, subject withdrawal, and logistical difficulty. Dose interruptions were also observed in 67 patients (19.0%) receiving placebo, including 47 for adverse events, 20 for subject error, and three each for site error and subject withdrawal. Dose reductions occurred for 121 patients (34.6%) in the sorafenib group, including 115 for adverse events, 14 for subject error, and 1 for site error; and for 22 (6.2%) in the placebo group, including 12 for adverse events, 11 for subject error, and 1 each for site error and logistical difficulty.

### Efficacy End Points

At the time of the analysis, 294 (84%) patients in the sorafenib group and 330 (94%) in the placebo group have shown disease progression and 285 (81%) and 294 (83%), respectively, have died.

The primary efficacy outcome, OS, did not differ significantly between the sorafenib and placebo groups (Fig. 2*A*; 8.2 versus 8.3 mo: HR, 0.99; 95% CI, 0.84–1.17; $p = 0.47$).

Patients in the sorafenib group had statistically significantly longer PFS (2.8 versus 1.4 mo; HR, 0.61; 95%

 

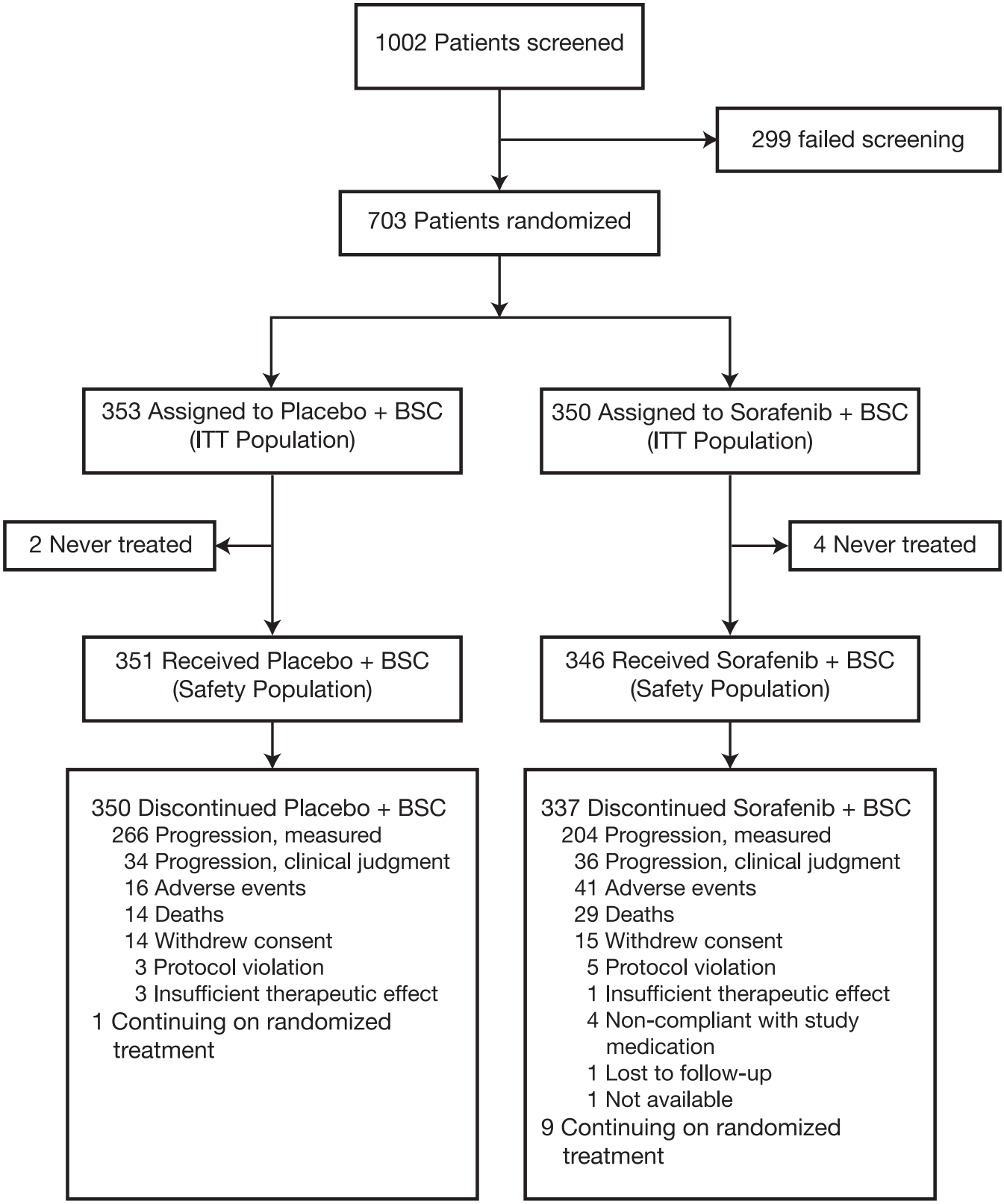


**FIGURE 1.** Patient disposition in the Monotherapy admInistration of Sorafenib in patientS wIth nOn–small-cell luNg cancer (MISSION) trial.

**TABLE 1.** Patient Demographics

| Demographic Characteristic, n (%) | Sorafenib (n = 350) | Placebo (n = 353) |
|---|---|---|
| Median age, yr | 59.0 | 62.0 |
| Geographic region | | |
| North America, Northern/Western Europe | 122 (34.9) | 119 (33.7) |
| South America/Eastern Europe/Asia-Pacific | 228 (35.1) | 234 (66.3) |
| Asia-Pacific (only) | 174 (49.7) | 172 (48.7) |
| Male | 186 (53.1) | 209 (59.2) |
| Smoking status | | |
| Nonsmoker | 161 (46.0) | 134 (38.0) |
| Past or present smoker | 181 (51.7) | 216 (61.2) |
| ECOG performance status | | |
| 0 | 110 (31.4) | 110 (31.2) |
| 1 | 233 (66.6) | 242 (68.6) |
| Brain metastases present | 56 (16.0) | 54 (15.3) |
| Number of previous regimens | | |
| 2 | 188 (53.7) | 197 (55.8) |
| 3 | 158 (45.1) | 153 (43.3) |
| Prior EGFR-based systemic therapy | 209 (59.7) | 207 (58.6) |

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

CI, 0.51–0.72; $p < 0.0001$; Fig. 2*B*) and TTP (2.9 versus 1.4 mo; HR, 0.54; 95% CI, 0.45–0.65; $p < 0.0001$; Fig. 2*C*) than patients in the placebo group.

Analysis of responses using RECIST criteria showed that none of the patients in either group achieved a complete response. A total of 17 patients (4.9%) in the sorafenib group and three (0.9%) in the placebo group achieved a PR. The ORR was significantly greater for the sorafenib group than for the placebo group (4.9% versus 0.9%, $p < 0.000001$; one-sided Cochran–Mantel–Haenszel test).

A total of 148 patients (42.3%) receiving sorafenib and 84 (24.3%) receiving placebo achieved SD. The DCR was significantly higher with sorafenib therapy than with placebo (47.1% versus 24.7%, $p = 0.00086$; one-sided Cochran–Mantel–Haenszel test).

Forest plots comparing outcomes showed no differences in OS, PFS, and TTP in the analyzed subgroups (Fig. 3; Supplementary Tables 1A–C, Supplementary Digital Content, http://links.lww.com/JTO/A906).

## Poststudy Anticancer Therapy

Poststudy therapy was administered to 154 (44.0%) patients in the sorafenib group and 198 (56.1%) in the placebo

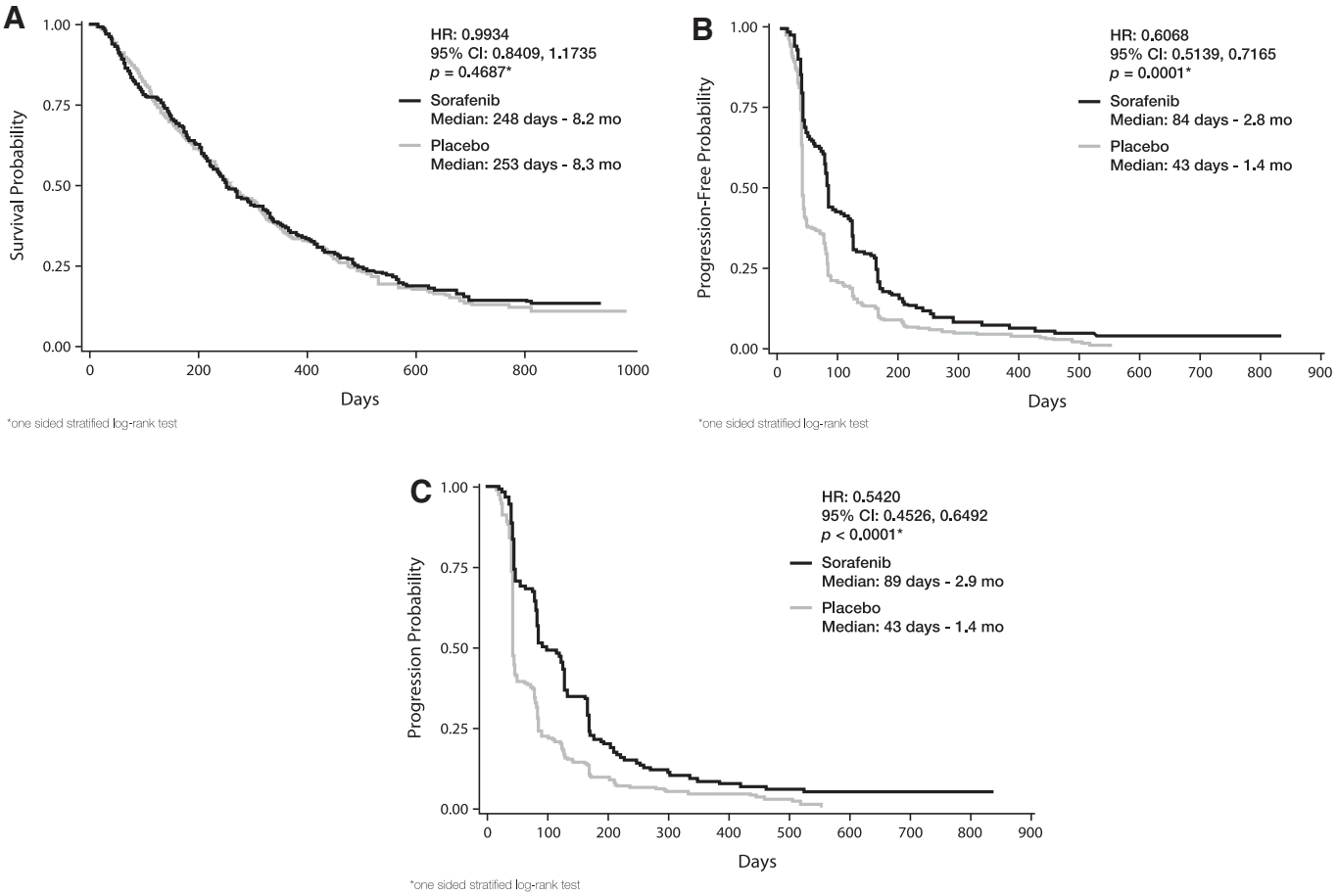


**FIGURE 2.** Kaplan–Meier analyses of (A) overall survival, (B) progression-free survival, and (C) time to progression in patients with non–small-cell lung cancer (NSCLC) receiving sorafenib or placebo as third-/fourth-line treatment.

 

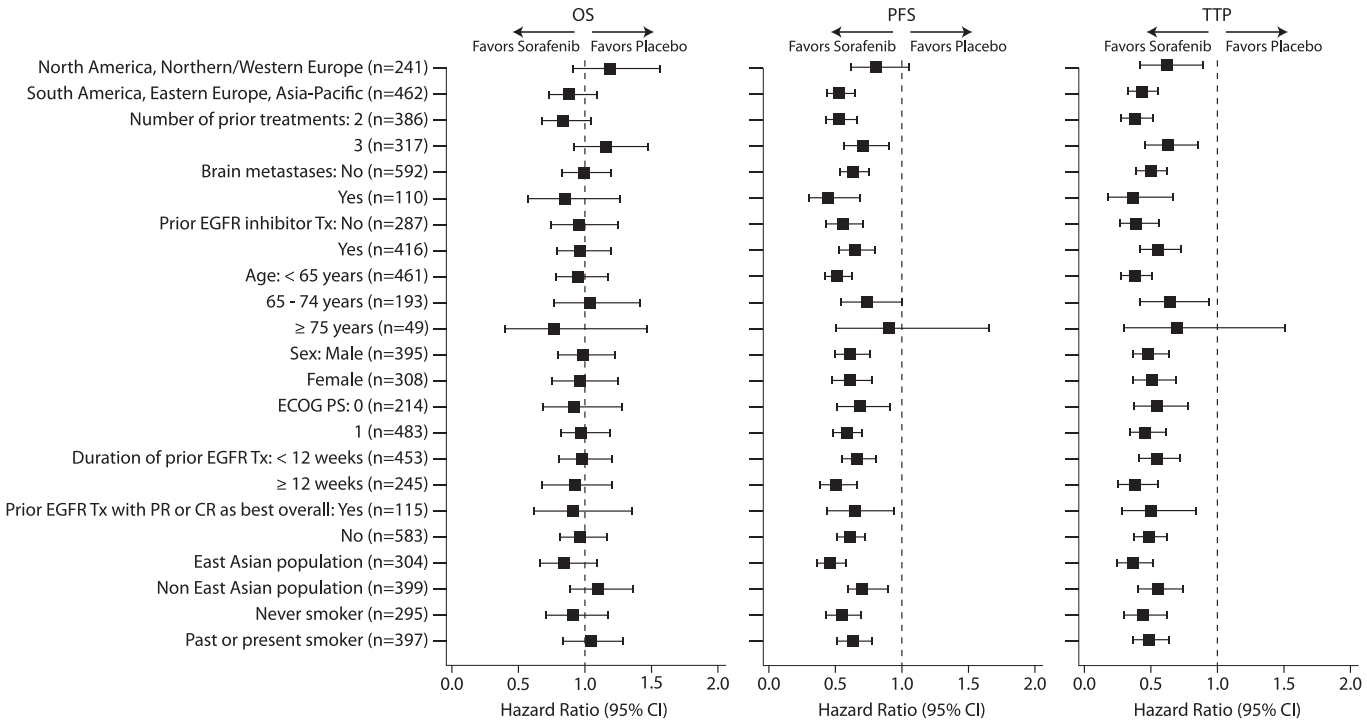


**FIGURE 3.** Subgroup analysis for overall survival, progression-free survival, and time to progression.

group. Of the patients in these two groups, 151 (43.1%) and 198 (56.1%) received one or more additional regimens; 62 (17.7%) and 78 (22.1%), respectively, received two or more additional regimens; and 27 (7.7%) and 31 (8.8%), respectively, received three or more additional regimens; with some patients receiving as many as seven additional treatment regimens. Anti-EGFR agents were administered to 56 (16.9%) patients in the sorafenib and 74 (21.0%) in the placebo group; antimetabolites to 67 (19.1%) and 94 (26.6%), respectively; platinum compounds to 39 (11.1%) and 47 (13.3%), respectively; docetaxel, paclitaxel, or taxanes to 28 (8.0%), 5 (1.4%), or 12 (3.4%) and 34 (9.6%), 9 (2.5%), or 24 (6.8%), respectively; and vinca alkaloids to 34 (9.7%) and 35 (9.9%), respectively. Best reported outcomes in the sorafenib group included PR in 17 patients (4.9%) and SD in 49 (14.0%), whereas best reported outcomes in the placebo group included PR in 20 patients (5.7%) and SD in 75 (21.2%).

## Biomarker Analysis

Samples for biomarker testing were available for 347 of the 703 patients, including from 166 patients randomized to sorafenib and 181 randomized to placebo. Archival tumor samples were available from 90 patients. OS and PFS results in these patients were similar to those for the overall trial population; i.e., OS did not differ significantly, whereas PFS was significantly longer in patients randomized to sorafenib than to placebo (Fig. 4*A* and *B*).

Of the patients who provided samples for biomarker testing, 89 had EGFR mutations, including 44 randomized to sorafenib and 45 to placebo. The demographic and clinical characteristics of this subpopulation differed somewhat from that of patients with wild-type EGFR (Supplementary Table 2, Supplementary Digital Content, http://links.lww.com/JTO/A906). Patients with EGFR mutations were younger, were more likely to be female and nonsmokers, and were more likely to have brain metastases and to have received prior EGFR tyrosine kinase inhibitors. Among the patients with EGFR mutations, those receiving sorafenib had significantly longer OS (13.9 versus 6.5 months; HR, 0.48; 95% CI, 0.30–0.76, $p = 0.002$) and PFS (2.7 versus 1.4 months; HR, 0.27; 95% CI, 0.16–0.46, $p < 0.001$) than those receiving placebo (Fig. 4*C* and *D*). Although PFS was also significantly longer in patients with wild-type EGFR who received sorafenib than placebo (2.7 versus 1.5 months; HR, 0.62; 95% CI, 0.48–0.82, $p < 0.001$), OS was similar (8.3 versus 8.4 months; HR, 0.92; 95% CI, 0.70–1.21, $p = 0.559$). DCRs were higher with sorafenib than placebo in patients with EGFR mutations (40.9% versus 2.2%) and EGFR wild-type (46.7% versus 25.8%), whereas ORRs were slightly higher with sorafenib than placebo in patients with EGFR mutations (6.8% versus 0%) and EGFR wild-type (7.4% versus 1.5%) (Supplementary Table 3, Supplementary Digital Content, http://links.lww.com/JTO/A906). Biomarker treatment interaction analysis for EGFR yielded *p* values of 0.023 for OS and 0.015 for PFS.

Of the patients who provided samples for biomarker testing, 68 had KRAS mutations, 34 randomized to sorafenib, and 34 to placebo. PFS was significantly longer with sorafenib than placebo in patients with KRAS mutations (2.6 versus 1.7 mo; HR, 0.46; 95% CI, 0.25–0.82; $p = 0.007$) and wild-type KRAS (2.7 versus 1.4 mo; HR, 0.58; 95% CI, 0.45–0.75; $p < 0.001$) (Supplementary Fig. 1A and B, Supplementary Digital Content, http://links.lww.com/JTO/A906). OS, however, was

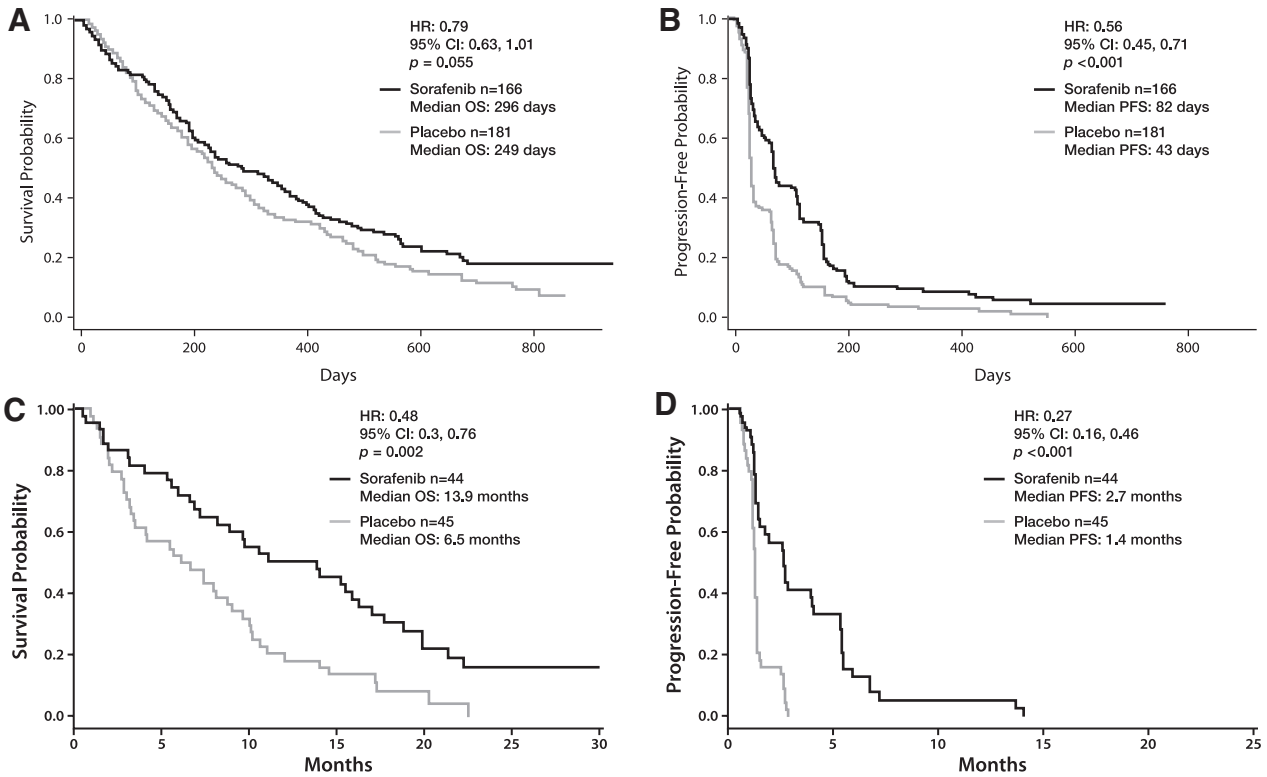


**FIGURE 4.** Overall survival (OS) and progression-free survival (PFS) among patients providing samples for biomarker analysis. (A) OS, (B) PFS, (C) OS for patients with epidermal growth factor receptor (EGFR) mutations, and (D) PFS for patients with EGFR mutations.

similar in patients in the sorafenib and placebo groups with KRAS mutations (6.4 versus 5.1 mo; HR, 0.76; 95% CI, 0.45–1.26; $p = 0.279$) and wild-type KRS (11.0 versus 9.1 mo; HR, 0.79; 95% CI, 0.60–1.03; $p = 0.078$) (Supplementary Fig. 1C and D, Supplementary Digital Content, http://links.lww.com/JTO/A906). DCRs were higher with sorafenib than placebo in patients with KRAS mutations (44.1% versus 7.6%) and KRAS wild-type (45.4% versus 20.4%), whereas ORRs were slightly higher with sorafenib than placebo in patients with KRAS mutations (2.9% versus 0%) and KRAS wild-type (8.3% versus 1.4%) (Supplementary Table 3, Supplementary Digital Content, http://links.lww.com/JTO/A906). Biomarker treatment interaction analysis for KRAS yielded $p$ values of 0.743 for OS and 0.696 for PFS.

## Safety

The overall incidence of treatment-emergent and drug-related treatment-emergent adverse events, including those considered serious, tended to be greater for the sorafenib than for the placebo group (Table 2). Table 3 shows the incidence of treatment-emergent AEs with frequency greater than 10% in either group, and Supplementary Table 4 (Supplementary Digital Content, http://links.lww.com/JTO/A906) shows the incidence of drug-related treatment-emergent adverse events occurring in more than 5% of either treatment group. No unexpected treatment-emergent adverse events or other safety outcomes occurred.

## DISCUSSION

Current treatment options for patients with relapsed/refractory NSCLC beyond the second line are limited. This multicenter, multinational, randomized, double-blind, placebo-controlled trial showed that third-/fourth-line sorafenib monotherapy plus BSC did not increase OS compared with placebo plus BSC among patients with nonsquamous NSCLC. Sorafenib monotherapy enhanced PFS, TTP, ORR, and DCR compared with placebo, but these effects were modest for the overall population. Safety and tolerability findings from this trial were consistent with the profile of sorafenib.

Analysis of patient demographic subgroups failed to demonstrate any survival advantage for sorafenib in any subgroup addressed, including prior number of treatments, presence/absence of brain metastases, prior EGFR inhibitor treatment, and smoking status. PFS was significantly greater in East Asian than in non-East Asians receiving sorafenib, although the hazard ratio for these two subgroups was relatively small.

Sorafenib showed significant survival benefits among patients with known EGFR mutations, with an increase in median OS of 7.3 months compared with placebo (HR, 0.48; 95% CI, 0.3–0.76; $p = 0.002$) and an increase in median PFS of 1.3 months (HR, 0.27; 95% CI, 0.16–0.46; $p < 0.001$). These results suggested that sorafenib is more effective in patients with EGFR mutations than with EGFR wild type. The recent finding that PFS was significantly longer in NSCLC patients with EGFR mutations who were treated with the combination of erlotinib

 

**TABLE 2.** Overview of Adverse Events

| Event, n (%) | CTC Grade | Sorafenib (n = 346) | Placebo (n = 351) |
|---|---|---|---|
| TEAEs | All | 342 (98.8) | 318 (90.6) |
| | 3 | 139 (40.2) | 66 (18.8) |
| | 4 | 14 (4.0) | 24 (6.8) |
| | 5 | 80 (23.1) | 46 (13.1) |
| Drug-related TEAEs | All | 304 (87.9) | 179 (49.3) |
| | 3 | 127 (36.7) | 18 (5.1) |
| | 4 | 6 (1.7) | 6 (1.7) |
| | 5 | 5 (1.4) | 0 |
| Serious TEAEs | All | 135 (39.0) | 111 (31.6) |
| | 3 | 36 (10.3) | 36 (10.3) |
| | 4 | 10 (2.9) | 18 (5.1) |
| | 5 | 80 (23.1) | 46 (13.1) |
| Serious drug-related TEAEs | All | 28 (8.1) | 11 (3.1) |
| | 3 | 16 (4.6) | 2 (0.6) |
| | 4 | 6 (1.7) | 5 (1.4) |
| | 5 | 5[a] (1.4) | 0 |

CTC, common technology criteria; TEAE, treatment-emergent adverse event.
[a]Includes two patients with CNS ischemia, one patient with cardiac ischemia/infarction, one patient with constitutional symptoms (other), and one patient with infection (other).

and the anti-VEGF antibody bevacizumab than erlotinib alone (16.0 versus 9.7 mo; HR, 0.54; 95% CI, 0.36–0.79; $p = 0.0015$), suggests a mechanism of action of sorafenib in NSCLC patients with EGFR mutations.[17] Future studies on combinations of EGFR TKIs and anti-angiogenic agents are warranted.

We found that sorafenib significantly enhanced PFS relative to placebo but had no effect on OS. Similar results were observed in patients with advanced NSCLC who were treated with the tyrosine kinase inhibitors afatinib and vandetanib. For example, the phase IIb/III LUX-Lung1 trial randomized 585 patients to second- or third-line treatment with afatinib (n = 390) or placebo (n = 195).[18] Afatinib significantly enhanced PFS versus placebo (3.3 versus 1.1 mo; HR, 0.38; 95% CI, 0.31–0.48; $p < 0.0001$) but had no effect on OS (10.8 versus 12.0 mo; HR, 1.08; 95% CI, 0.86–1.35; $p = 0.74$). In addition, the phase III ZEPHYR trial, which randomized 924 patients to receive vandetanib (n = 617) or placebo (n = 307), found that vandetanib significantly enhanced PFS (1.9 versus 1.8 mo; HR, 0.63; 95% CI, 0.54–0.74; $p < 0.001$) but did not affect OS (8.5 versus 7.8 mo; HR, 0.95; 95% CI, 0.81–1.11; $p = 0.527$).[19] These differences may be due to differences in poststudy treatments. In the LUX-Lung 1 study, for example, 24% of patients in the placebo arm, but only 12% in the afatinib, received poststudy EGFR TKIs.[18] The percentage of patients receiving poststudy treatments was higher in the placebo than in the sorafenib group (56.4% versus 44.0%). In addition, higher percentages of patients in the placebo than in the sorafenib group received more poststudy treatment regimens and were treated with certain classes of drugs, including anti-EGFR agents, antimetabolites, and taxanes. The DCR in response to these additional treatment regimens was higher in the placebo than in the sorafenib group, but the difference was not statistically significant.

The biomarker results of this trial were intriguing, suggesting that EGFR mutation may be a predictive biomarker for the efficacy of sorafenib in patients with advanced

**TABLE 3.** Treatment-Emergent Adverse Events Occurring in More Than 10% of Either Treatment Group

| | Sorafenib (n = 346) | | | Placebo (n = 351) | | |
|---|---|---|---|---|---|---|
| Event, n (%) | All | Grade 3 | Grade 4 | All | Grade 3 | Grade 4 |
| HFSR | 191 (55.2) | 56 (16.2) | 0 | 21 (6.0) | 2 (0.6) | 0 |
| Rash/desquamation | 140 (40.5) | 14 (4.0) | 0 | 43 (12.3) | 0 | 0 |
| Fatigue | 125 (36.1) | 29 (8.4) | 1 (0.3) | 97 (27.6) | 15 (4.3) | 0 |
| Diarrhea | 124 (35.8) | 11 (3.2) | 0 | 42 (12.0) | 1 (0.3) | 0 |
| Anorexia | 105 (30.3) | 11 (3.2) | 0 | 62 (17.7) | 8 (2.3) | 0 |
| Dyspnea | 97 (28.0) | 19 (5.5) | 6 (1.7) | 105 (29.9) | 19 (5.4) | 6 (1.7) |
| Cough | 78 (22.5) | 8 (2.3) | 0 | 68 (19.4) | 0 | 0 |
| Hypertension | 68 (19.7) | 18 (5.2) | 1 (0.3) | 16 (4.6) | 2 (0.6) | 0 |
| Alopecia | 65 (18.8) | 0 | 0 | 4 (1.1) | 0 | 0 |
| Nausea | 59 (17.1) | 6 (1.7) | 0 | 56 (16.0) | 3 (0.9) | 0 |
| Mucositis, oral cavity | 58 (16.8) | 3 (0.9) | 0 | 15 (4.3) | 0 | 0 |
| Hemorrhage/bleeding | 56 (16.2) | 3 (0.9) | 0 | 39 (11.1) | 2 (0.6) | 0 |
| Vomiting | 51 (14.7) | 5 (1.4) | 0 | 44 (12.5) | 3 (0.9) | 0 |
| Constipation | 49 (14.2) | 3 (0.9) | 0 | 48 (13.7) | 3 (0.9) | 0 |
| Pain, chest/thorax NOS | 45 (13.0) | 11 (3.2) | 0 | 33 (9.4) | 5 (1.4) | 0 |
| Weight loss | 43 (12.4) | 3 (0.9) | 0 | 17 (4.8) | 0 | 0 |
| Fever | 40 (11.6) | 0 | 0 | 19 (5.4) | 0 | 0 |
| Headache | 37 (10.7) | 3 (0.9) | 0 | 26 (7.4) | 3 (0.9) | 0 |
| Pain, abdomen NOS | 36 (10.4) | 4 (1.2) | 0 | 14 (4.0) | 5 (1.4) | 0 |
| Pain, back | 33 (9.5) | 6 (1.7) | 0 | 39 (11.1) | 4 (1.1) | 0 |

HFSR, hand-foot skin reaction; NOS, not otherwise specified.

NSCLC. Statistically significant positive interactions were observed for both PFS and OS, although the OS outcome may have been biased by poststudy treatment with EGFR TKIs. Analysis showed that, of patients with EGFR mutations, 19 of 44 (43%) in the sorafenib group and 8 of 45 (18%) in the placebo group were treated with EGFR TKIs after the end of this trial (data not shown). In contrast to EGFR, KRAS mutation status did not seem to influence response to sorafenib. Negative interaction analyses were observed for both PFS and OS. Sorafenib significantly enhanced PFS, relative to placebo, in patients with both KRAS mutant and wild type. Our biomarker results should be interpreted with caution, however, especially because the subgroup of patients with available samples for biomarker analysis constituted only 47% and was not representative of the overall study population. In addition, biomarker analyses in this trial were performed retrospectively. New approaches, such as proteomic mass spectrometry, are being explored to identify patients with advanced NSCLC likely to benefit from treatment with targeted therapies.[20–25]

In conclusion, sorafenib monotherapy plus BSC as third- or fourth-line treatment did not enhance OS over placebo plus BSC in patients with advanced/refractory NSCLC. Statistically significant but clinically modest increases in PFS, TTP, ORR, and DCR were observed. Safety and tolerability were consistent with the known profile of this agent. Treatment options for patients needing third- and fourth-line therapy for NSCLC remain an unmet medical need.

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## REFERENCES

1. Langer CJ, Mok T, Postmus PE. Targeted agents in the third-/fourth-line treatment of patients with advanced (stage III/IV) non-small cell lung cancer (NSCLC). *Cancer Treat Rev* 2013;39:252–260.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). *Non-Small Cell Lung Cancer. 2012;v1.2013*. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed December 7, 2012.
3. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004;64:7099–7109.
4. Escudier B, Eisen T, Stadler WM, et al.; TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–134.
5. Llovet JM, Ricci S, Mazzaferro V, et al.; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390.
6. Blumenschein GR Jr, Gatzemeier U, Fossella F, et al. Phase II, multicenter, uncontrolled trial of single-agent sorafenib in patients with relapsed or refractory, advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:4274–4280.
7. Wakelee HA, Lee JW, Hanna NH, Traynor AM, Carbone DP, Schiller JH. A double-blind randomized discontinuation phase-II study of sorafenib (BAY 43-9006) in previously treated non-small-cell lung cancer patients: eastern cooperative oncology group study E2501. *J Thorac Oncol* 2012;7:1574–1582.
8. Smit EF, Dingemans AM, Thunnissen FB, Hochstenbach MM, van Suylen RJ, Postmus PE. Sorafenib in patients with advanced non-small cell lung cancer that harbor K-ras mutations: a brief report. *J Thorac Oncol* 2010;5:719–720.
9. Dingemans AM, Mellema WW, Groen HJ, et al. A phase II study of sorafenib in patients with platinum-pretreated, advanced (Stage IIIb or IV) non-small cell lung cancer with a KRAS mutation. *Clin Cancer Res* 2013;19:743–751.
10. Kim ES, Herbst RS, Wistuba II, et al. The BATTLE trial: personalizing therapy for lung cancer. *Cancer Discov* 2011;1:44–53.
11. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25–34.
12. Scagliotti G, Novello S, von Pawel J, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:1835–1842.
13. Therasse P, Arbuck SG, Eisenhauer EA, 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;92:205–216.
14. Dressman D, Yan H, Traverso G, Kinzler KW, Vogelstein B. Transforming single DNA molecules into fluorescent magnetic particles for detection and enumeration of genetic variations. *Proc Natl Acad Sci U S A* 2003;100:8817–8822.
15. Diehl F, Li M, Dressman D, et al. Detection and quantification of mutations in the plasma of patients with colorectal tumors. *Proc Natl Acad Sci U S A* 2005;102:16368–16373.
16. Taniguchi K, Uchida J, Nishino K, et al. Quantitative detection of EGFR mutations in circulating tumor DNA derived from lung adenocarcinomas. *Clin Cancer Res* 2011;17:7808–7815.
17. Kato T, Seto T, Nishio M, et al. Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation-positive nonsquamous non-small cell lung cancer (NSCLC): an open-label randomized trial. *J Clin Oncol* 2014;32(15 Suppl):8005 (abstract).
18. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012;13:528–538.
19. Lee JS, Hirsh V, Park K, et al. Vandetanib Versus placebo in patients with advanced non-small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: a randomized, double-blind phase III trial (ZEPHYR). *J Clin Oncol* 2012;30:1114–1121.
20. Amann JM, Lee JW, Roder H, et al. Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 3503. *J Thorac Oncol* 2010;5:169–178.
21. Carbone DP, Salmon JS, Billheimer D, et al. VeriStrat classifier for survival and time to progression in non-small cell lung cancer (NSCLC) patients treated with erlotinib and bevacizumab. *Lung Cancer* 2010;69:337–340.
22. Carbone DP, Ding K, Roder H, et al. Prognostic and predictive role of the VeriStrat plasma test in patients with advanced non-small-cell lung cancer treated with erlotinib or placebo in the NCIC Clinical Trials Group BR.21 trial. *J Thorac Oncol* 2012;7:1653–1660.
23. Gautschi O, Dingemans AM, Crowe S, et al. VeriStrat® has a prognostic value for patients with advanced non-small cell lung cancer treated with erlotinib and bevacizumab in the first line: pooled analysis of SAKK19/05 and NTR528. *Lung Cancer* 2013;79:59–64.
24. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. *Lancet Oncol*. 2014;15:713–721.
25. Kuiper JL, Lind JS, Groen HJ, et al. VeriStrat(®) has prognostic value in advanced stage NSCLC patients treated with erlotinib and sorafenib. *Br J Cancer* 2012;107:1820–1825.

 