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A randomized, double-blind, phase II study of erlotinib with or without sunitinib for the second-line treatment of metastatic non-small-cell lung cancer (NSCLC)

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Background: Combined inhibition of vascular, platelet-derived, and epidermal growth factor receptor (EGFR) pathways may overcome refractoriness to single agents in platinum-pretreated non-small-cell lung cancer (NSCLC).
Patients and methods: This randomized, double-blind, multicenter, phase II trial evaluated sunitinib 37.5 mg/day plus erlotinib 150 mg/day versus placebo plus erlotinib continuously in 4-week cycles. Eligible patients had histologically confirmed stage IIIB or IV NSCLC previously treated with one or two chemotherapy regimens, including one platinum-based regimen. The primary end point was progression-free survival (PFS) by an independent central review.
Results: One hundred and thirty-two patients were randomly assigned, and the median duration of follow-up was 17.7 months. The median PFS was 2.8 versus 2.0 months for the combination versus erlotinib alone (HR 0.898, $P = 0.321$). The median overall survival (OS) was 8.2 versus 7.6 months (HR 1.066, $P = 0.617$). Objective response rates (ORRs) were 4.6% and 3.0%, respectively. Sunitinib plus erlotinib was fairly well tolerated although most treatment-related adverse events (AEs) were more frequent than with erlotinib alone: diarrhea (55% versus 33%), rash (41% versus 30%), fatigue (31% versus 25%), decreased appetite (30% versus 13%), nausea (28% versus 14%), and thrombocytopenia (13% versus 0%).
Conclusions: The addition of sunitinib to erlotinib did not significantly improve PFS in patients with advanced, platinum-pretreated NSCLC.
Key words: combination therapy, efficacy, erlotinib, non-small-cell lung cancer, safety, sunitinib

introduction

Treatments of advanced non-small-cell lung cancer (NSCLC) typically include platinum-based chemotherapy with or without a vascular endothelial growth factor (VEGF)-targeted monoclonal antibody [1]. Second-line treatments including the epidermal growth factor receptor (EGFR) inhibitor erlotinib are associated with modest prolongation of survival [2, 3]. Consequently novel treatment strategies for advanced NSCLC are required.

VEGFR and platelet-derived growth factor receptor (PDGFR) pathways are implicated in the pathogenesis of NSCLC. VEGFR-2 is the primary receptor involved in endothelial cell proliferation and migration, while VEGFR-3 plays a role in angiogenic sprouting and lymphangiogenesis, and PDGFR-α and -β are implicated in the growth and survival of vascular smooth muscle cells and pericytes [4–6]. The EGFR pathway has also been linked to cell proliferation, angiogenesis, and metastasis [7].

Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor (TKI) of VEGFR-1, -2, and -3, PDGFR-α, PDGFR-β, stem-cell factor receptor (KIT), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF-1R), and glial cell line-derived neurotrophic factor receptor (Rearranged

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during Transfection; RET) [8–13]. In a phase II trial, single-agent sunitinib provided clinical benefit with acceptable tolerability in patients with advanced, platinum-refractory NSCLC [14, 15].

Given the heterogeneity of NSCLC and potential crosstalk between signaling pathways implicated in tumor growth, angiogenesis and metastasis, combining targeted agents could improve the efficacy over single-target agents, and data from NSCLC xenograft models suggest that sunitinib may augment the antitumor activity of erlotinib [13, 16].

We conducted a randomized, double-blind, multicenter, phase II trial to evaluate the addition of sunitinib to erlotinib in patients with platinum-pretreated NSCLC. Data from 30 patients in lead-in cohorts of this study indicated acceptable safety and evidence of antitumor activity [17]. Here, we present the results of the randomized, phase II component of this trial (NCT00265317).

methods

patients

Patients ≥18 years old had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and histologically confirmed stage IIIB (with malignant effusion) or IV NSCLC previously treated with one or two chemotherapy regimens, including one platinum-based regimen. Prior treatment with TKIs (except insulin-like growth factor receptor inhibitors) or cetuximab was not permitted. The exclusion criteria included a history of or current brain metastases or spinal cord compression, inadequate hepatic, hematologic or renal function, hemoptysis within 4 weeks before starting study treatment; uncontrolled hypertension and clinically significant cardiovascular disease during the preceding 12 months.

All patients provided written informed consent. The study was approved by the institutional review board of each center and carried out in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, and applicable local laws and regulatory requirements.

study design and treatment

Patients received sunitinib 37.5 mg/day on a continuous once-daily dosing schedule (or placebo) plus erlotinib 150 mg/day, in repeated 4-week cycles. Treatment was continued until the Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression, unacceptable toxicity, or for up to 18 cycles (after which treatment assignment was unblinded and open-label access to sunitinib was offered).

The primary end point of the double-blind phase was progression-free survival (PFS) assessed by an independent central radiologic review. Secondary end points included objective response rates (ORRs), duration of response, 1-year survival, overall survival (OS), safety, patient-reported outcomes (PROs), and associations between biomarkers and treatment outcome.

Randomization (1:1) was stratified by smoking history (never versus prior versus current) and EGFR status determined by immunohistochemistry or fluorescence *in situ* hybridization (positive versus negative versus unmeasured). A centralized randomization procedure (interactive response system accessible via telephone or internet) assigned patients to each treatment using a blocked randomization with a block size of 4 within each stratum. Patients, investigators, and the trial study team were blinded to treatment assignments.

study assessments

Tumor imaging by computed tomography or magnetic resonance was carried out at baseline, 8 and 12 weeks from the start of study medication, and every 8 weeks thereafter and whenever disease progression was suspected or to confirm response. Brain and bone scans were carried out at baseline and repeated if clinically indicated (regularly scheduled bone scans were required if bone metastases were present at baseline). Response measurements were carried out according to RECIST (version 1.0) [18]. PFS was defined as the time from randomization to the first documentation of objective tumor progression or death from any cause. The ORR was defined as the percentage of subjects with confirmed complete response (CR) or partial response (PR) relative to all randomly assigned patients. The duration of response was the time from first documentation of objective response to the time of tumor progression or death. One-year survival probability was based on Kaplan–Meier estimates from the date of randomization.

Safety was evaluated throughout the study for all patients receiving at least one dose of study treatment by assessment of adverse events [AEs; National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0], laboratory abnormalities, physical examinations, electrocardiograms, and either multi-gated acquisition scans using red blood cells labeled with technetium-99m-pertechnate, or echocardiograms (carried out at baseline and as clinically indicated). PROs were measured each cycle using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and supplemental lung cancer module (QLQ-LC13).

Exploratory analyses of tumor biopsies were established *pre-hoc* and included: immunohistochemistry for EGFR, *EGFR* gene copy number, *EGFR* (exons 18–21), and *KRAS* (exons 2 and 3, including codons 12, 13, and 61) mutational status, and mRNA expression profiling via multiplex XP-RT-PCR™ of gene transcripts relating to angiogenesis and tumor growth as well as targets of sunitinib [CSF-1R, PDGFR-α, PDGFR-β, KIT, FLT3], RET, VEGFR-1, VEGFR-2 and VEGFR-3, FGF (fibroblast growth factor), VEGF, and VEGF-C]. Methodological details are presented in the supplementary information, available at *Annals of Oncology* online.

Plasma samples were collected before dosing on day 1 of cycles 1–3 and stored at −70°C before analysis. Storage duration was within the period covered by stability evaluation for each analyte. VEGF-C, soluble (s) VEGFR-2, sVEGFR-3, and sKIT were analyzed under Good Laboratory Practice conditions using a validated enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN).

statistical analysis

The study was powered to detect a 50% improvement in median PFS from 10 weeks in the erlotinib alone arm to 15 weeks in the sunitinib plus erlotinib arm [3]. The target sample size was 126 patients, and 115 events were required to confer 80% power with a one-sided alpha of 0.1. An interim analysis of efficacy and safety was planned at 58 PFS events.

Efficacy end points and patient characteristics were evaluated in all randomly assigned patients (full analysis population). Treatment administration and safety were evaluated in all randomly assigned patients who received at least one dose of study medication (safety population). Response-related end points (PFS, ORR, and duration of response) were based on the independent, central review of tumor data.

PFS and OS were summarized using the Kaplan–Meier method; between-treatment comparisons for PFS and OS were conducted using one-sided log-rank tests. The Cox regression model was used to estimate hazard ratios (HRs) with two-sided 80% and 95% confidence intervals (CI) for PFS and OS, respectively. Log-rank tests and Cox regression models were used to explore the potential influences of patient/disease characteristics on PFS and OS. ORRs were compared between the treatment arms using Chi-square

tests. Descriptive statistics were used for treatment administration and safety. Descriptive statistics and 95% CI for changes from baseline were calculated for PROs.

The significance of changes in soluble protein levels from baseline (expressed as ratios to baseline) was determined using the Wilcoxon signed–rank test. Concentrations of soluble proteins at baseline, and ratios to baseline at each time point, were compared between the treatment arms using the Wilcoxon rank sum test.

results

patient characteristics and dosage

In total, 132 patients were randomized between January 2007 and January 2009, at 24 centers in the USA, Canada and Europe, and 64 patients were treated in each arm (Figure 1). Patient and tumor characteristics were balanced between arms, including *EGFR* gene copy number, amplification, and mutational status (Table 1). The most common histologies were adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. Most patients had received one prior chemotherapy (64.4%) or two prior chemotherapies (33.3%). Patients received a median of three treatment cycles in both the study arms; most dose delays, reductions and interruptions were attributed to AEs. There were more dose reductions and dose interruptions with the combination than with erlotinib treatment alone (Table 2).

antitumor activity

The median follow-up was 17.7 months. Of 115 planned PFS events, only 78 ($n = 36$ for the combination, $n = 42$ for erlotinib alone) were observed based on the central third-party review. The number was lower than expected due to a greater than anticipated dropout rate (balanced between the study arms) and withdrawal of subjects based on investigator-assessed disease progression that was not subsequently confirmed by a central review. The reasons for dropout included AEs (9%), protocol violations (4%), global deterioration of health status (2%), refusal to continue treatment for reason other than AE (2%), and lost to follow–up (1%). Withdrawals due to investigator-assessed progression not subsequently confirmed occurred in 12 subjects on the combination arm and 6 subjects on the erlotinib arm. Median PFS was 2.8 months [95% confidence interval (CI) 1.9–4.5] for the combination and 2.0 months (95% CI 1.8–2.8) for erlotinib [HR 0.898 (80% CI 0.671–1.203, $P = 0.321$; Figure 2].

The median OS was 8.2 months (95% CI 5.7–11.3) for the combination and 7.6 months (95% CI 5.3–13.4) for erlotinib (HR 1.066; 95% CI 0.705–1.612, $P = 0.617$). Approximately 30% of patients were censored in the analysis, primarily because they were in follow-up at the time of data cut-off. The probability of survival at 1 year was 0.32 (95% CI 0.197–0.443) and 0.42 (95% CI 0.301–0.542), respectively. No patient subsets had statistically significant improvements in PFS or OS.

The ORR was 4.6% (95% CI 0.96–12.90) for the combination and 3.0% (95% CI 0.36–10.37) for erlotinib ($P = 0.624$); no CR was observed. Durations of responses (censored at the time of analysis) were 14.1+, 3.6+, and 1.0+ months for the three patients with PR in the combination arm and 10.9+ and 3.7+ months for the two patients with PRs in the erlotinib arm. One of these patients (the 14.1+ month responder) had a confirmed *EGFR* mutation; the others were wild-type, indeterminate or not reported.

safety

Combination treatment was associated with more severe side effects than erlotinib alone, particularly grade 3 toxic effects. With the combination, the most common treatment-related AEs were diarrhea, rash, and fatigue. With erlotinib, the incidence of fatigue was similar, while diarrhea and rash were less frequent (Table 3). Other treatment-related AEs that differed between the study arms included: decreased appetite, nausea, thrombocytopenia, and pruritus. Two treatment-related grade 4 AEs occurred with the combination [ischemia and thrombocytopenia (reported as an AE but not noted in the hematologic laboratory data; supplementary Table 1, available at *Annals of Oncology* online)]; three grade 4 treatment-related AEs occurred with erlotinib (ulcer hemorrhage, dehydration, and pulmonary embolism).

Treatment-related serious AEs included diarrhea [combination: 8% (grade 3); erlotinib: 2% (grade 3)], gastrointestinal hemorrhage [combination only: 2% (grade 2), 2% (grade 3)], and dehydration [erlotinib only: 2% (grade 3), 2% (grade 4)].

Treatment-related AEs resulting in study discontinuation were fatigue, nausea, acute pancreatitis, thrombocytopenia, ischemia, diarrhea, esophagitis, and pulmonary hemorrhage ($n = 1$ each) for the combination; and alveolar proteinosis, vomiting, and deep vein thrombosis ($n = 1$ each) for erlotinib.

There were 20 on-study deaths: 9 in the combination arm ($n = 8$ disease progression, $n = 1$ suicide) and 11 in the erlotinib arm ($n = 8$ disease progression, $n = 2$ cardiopulmonary failure, $n = 1$ pulmonary edema). All were judged to be unrelated to treatment. One patient in the combination arm died of intracranial hemorrhage 31 days after the last dose of study medication, which was considered treatment-related.

biomarker analysis

No significant differences in PFS were observed between the study arms according to tumor EGFR (assessed by protein expression, gene mutation, and gene copy number) or *KRAS* mutation status (Figure 3). In patients with *KRAS* mutations ($n = 6$ in the combination arm and $n = 4$ in the erlotinib arm), the HR for the addition of sunitinib was 0.481 (95% CI, 0.079–2.910). In patients with low (< median) tumor PDGFR-α RNA expression levels, PFS favored the combination ($n = 16$ versus $n = 11$; HR = 0.386, 95% CI: 0.127–1.173, one-sided $P = 0.040$, unadjusted for multiplicity).

Plasma levels of sVEGFR-2, sVEGFR-3, and sKIT decreased significantly from baseline with the combination ($P < 0.0001$), while no significant changes from baseline were observed with erlotinib (Supplementary Figure 1, available at *Annals of Oncology* online). With the combination, there were no significant differences in PFS for any soluble protein that was assessed. With erlotinib, PFS was significantly prolonged in patients with high (≥ median) baseline sKIT levels (HR = 0.406, $P = 0.005$), and in patients having low (< median) sVEGFR-3 ratios to baseline at cycle 2 day 1 (HR = 2.652, $P = 0.006$) and at cycle 3 day 1 (HR = 2.673, $P = 0.016$).

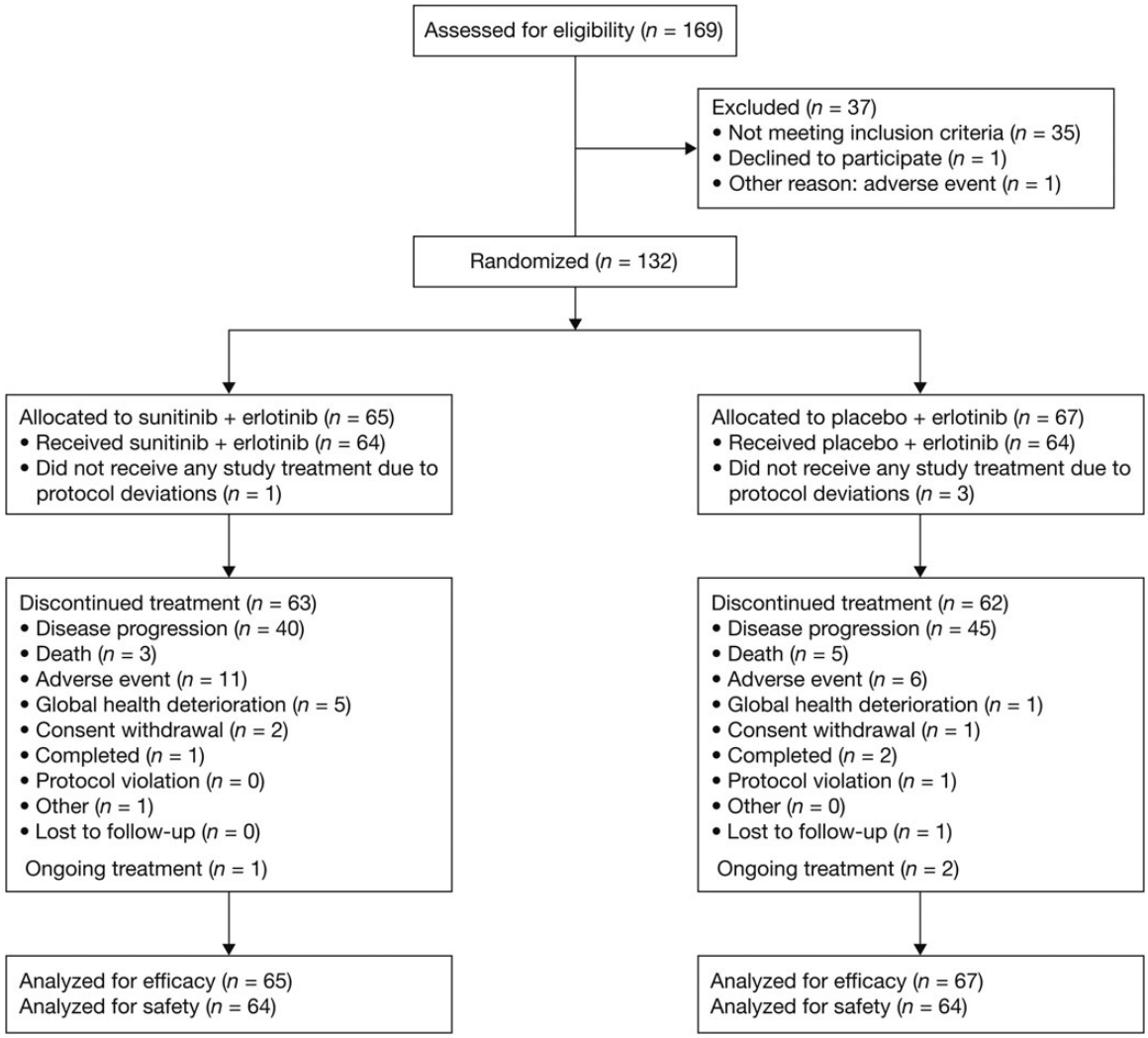


Figure 1. Patient disposition (CONSORT flow diagram).

The relationship between soluble protein levels and OS was explored in a *post hoc* analysis. In the combination arm, OS was significantly prolonged in patients with low (< median) baseline VEGF-C levels (HR = 2.105, $P = 0.033$; Supplementary Figure 2, available at *Annals of Oncology* online) and in patients with high (≥ median) sVEGFR-3 ratios to baseline at cycle 2 day 1 (HR = 0.435, $P = 0.038$). No other statistically significant associations between OS and soluble protein levels were observed.

patient-reported outcomes

There were no clinically or statistically significant changes in global health status, quality of life or functioning scales in either treatment arm, suggesting that global health-related quality of life and functioning were maintained for patients receiving sunitinib plus erlotinib (data not shown).

discussion

This phase II study did not demonstrate a PFS difference with sunitinib plus erlotinib (2.8 months, 95% CI 1.9–4.5) versus erlotinib alone (2.0 months, 95% CI 1.8–2.8) in patients with platinum-pretreated, advanced NSCLC (HR 0.898, $P = 0.321$). In addition, no significant difference was observed for OS (HR 1.066, 95% CI 0.705–1.612, $P = 0.617$). A recently reported phase III trial of sunitinib plus erlotinib in treatment-refractory advanced NSCLC also showed no significant effect on OS compared with erlotinib alone, but did demonstrate a significant improvement in PFS (a secondary end point) [19].

Exploratory analyses by clinical subsets indicated no effect of combination treatment on PFS. Additionally, there are currently no validated biomarkers that predict clinical activity with sunitinib treatment for NSCLC. BATTLE I, a phase II biomarker-driven study, suggested that patients with NSCLC and *KRAS* mutations may be more likely to benefit from treatment with sorafenib, while those with *EGFR* mutation/copy number gain may do worse [20]. Similarly, exploratory analyses in this study showed an HR of 0.481 for the addition of sunitinib in patients with *KRAS* mutations. However, the small number of subjects ($n = 10$) and the corresponding large confidence interval (0.079–2.910) limit confidence in the interpretation. Interestingly, a treatment-related difference in

Table 1. Patient and disease characteristics at baseline

Patient characteristic	Sunitinib + erlotinib ($n = 65$)	Placebo + erlotinib ($n = 67$)
Median age (range), years	59 (37–79)	61 (39–81)
Male, *n* (%)	39 (60)	45 (67)
Race, *n* (%)[a]		
Caucasian	63 (97)	64 (96)
Asian	1 (2)	2 (3)
Other	0	1 (1)
Smoking status, *n* (%)[b]		
Current	26 (40)	24 (36)
Prior	31 (48)	33 (49)
Never	7 (11)	9 (13)
Unknown	1 (2)	1 (1)
Eastern Cooperative Oncology Group performance status (ECOG PS), *n* (%)[c]		
0	21 (32)	21 (31)
1	43 (66)	45 (67)
Disease stage, *n* (%)[a]		
IIIB	1 (2)	0
IV	63 (97)	67 (100.0)
Histology, *n* (%)[a]		
Adenocarcinoma	36 (55)	29 (43)
Squamous cell carcinoma	15 (23)	19 (28)
Large cell carcinoma	6 (9)	10 (15)
Bronchioloalveolar carcinoma	0	2 (3)
Other/NOS	7 (11)	7 (10)
EGFR expression, *n* (%)		
Positive	29 (45)	36 (54)
Negative	19 (29)	12 (18)
Unmeasured[d]	17 (26)	19 (28)
EGFR gene copy number increased, *n* (%)		
Positive	0	1 (1)
Negative	31 (48)	28 (42)
Unmeasured[d]	34 (52)	38 (57)
EGFR gene amplification, *n* (%)		
No	31 (48)	29 (43)
Unmeasured	34 (52)	38 (57)
EGFR gene mutation, *n* (%)		
Mutated	4 (6)	1 (1)
Wild type	21 (32)	19 (28)
Indeterminate[d]	40 (62)	47 (70)
KRAS mutation status, *n* (%)		
Mutated	6 (9)	4 (6)
Wild type	22 (34)	19 (28)
Indeterminate[d]	37 (57)	44 (66)
Prior radiation therapy, *n* (%)		
Neoadjuvant	3 (5)	3 (4)
Adjuvant	6 (9)	3 (4)
Palliative	28 (43)	29 (43)
Prior surgery (resection or exploratory thoracotomy), *n* (%)	20 (31)	15 (22)
Prior chemotherapy, *n* (%)[a]		
1 regimen	39 (60)	46 (69)
2 regimens	23 (35)	21 (31)
≥3 regimens	1 (2)	0

[a]Data not collected from one subject in the sunitinib arm with no informed consent who was randomized in error.
[b]Current smoker includes subjects who stopped smoking <1 year before the first dose of study medication; prior smokers stopped smoking ≥1 year before the first dose of study medication.
[c]In the erlotinib arm, 1 patient had ECOG PS of 2.
[d]Includes patients where a tissue sample was not available ($n = 14$ for combination arm and $n = 14$ for erlotinib arm).
ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

PFS favoring the combination was observed for patients with low-tumor PDGFR-α RNA levels (HR 0.386, $P = 0.040$). Amplification of chromosomal segment 4q12 in NSCLC tumors has been previously attributed to *PDGFR-α* and *KIT* copy number gains, and *PDGFR-α* and *KIT* have been implicated as potential oncogenes [21]. The relevance of these findings requires additional investigation.

Plasma levels of sVEGFR-2, sVEGFR-3, and sKIT decreased significantly from baseline in the combination arm ($P < 0.0001$), but not in the erlotinib arm. These observations were consistent with studies of sunitinib in other tumor types [22–24], and suggest that sunitinib pharmacodynamics are not attenuated by co-administration with erlotinib. Comparable reductions in levels of these plasma proteins were not observed in patients treated with erlotinib alone, consistent with the target profile of this EGFR inhibitor. Interestingly, lower baseline levels of VEGF-C were associated with longer OS in patients receiving combination treatment, consistent with the association of low baseline levels of VEGF-C and longer PFS observed in sunitinib trials in RCC [25, 26].

Sunitinib plus erlotinib was fairly well tolerated, although grade 3 and 4 toxic effects were more common than with erlotinib alone. The most common AEs were consistent with previous reports from studies of single-agent sunitinib or erlotinib, and no unexpected AEs were observed [3, 14, 15]. Treatment-related AEs were more frequent with the combination than with erlotinib, including diarrhea, rash, anorexia, nausea, and thrombocytopenia. Dose delays, reductions, and interruptions therefore occurred more often in the combination arm.

Co-inhibition of VEGF and EGFR pathways in refractory NSCLC has been investigated in other clinical trials. Vandetanib, a dual VEGFR and EGFR inhibitor, was investigated in four phase III trials in combination with chemotherapy (pemetrexed or docetaxel) or best supportive care [27–30]. Only one of these trials, ZODIAC (vandetanib in combination with docetaxel as second-line therapy in patients with advanced NSCLC) met its primary end point of prolonging PFS compared with docetaxel alone [29]. However, there was no significant effect on OS. As with the ZEAL trial (vandetanib plus pemetrexed) [30], the OS results may have been confounded by differences between groups in post-progression therapies. Similarly, the addition of bevacizumab to erlotinib in

Table 2. Study drug exposure

	Sunitinib + erlotinib ($n = 64$)		Placebo + Erlotinib ($n = 64$)	
	Sunitinib	Erlotinib	Placebo	Erlotinib
Median cycles started (range)	3 (1–18)	3 (1–18)		
Median days study treatment administered (range)	58.5 (1–473)	59.0 (1–470)	84.5 (3–511)	84.0 (3–504)
Patients with cycle delays[a], *n* (%)	18 (28)	14 (22)	6 (9)	7 (11)
Cycle delays due to adverse events[b]	10 (16)	6 (9)	3 (5)	2 (3)
Patients with dose reductions, *n* (%)	15 (23)	14 (22)	6 (9)	7 (11)
Dose reductions due to adverse events[b]	13 (20)	13 (20)	6 (9)	6 (9)
Patients with dose interruptions[c], *n* (%)	17 (27)	18 (28)	9 (14)	11 (17)
Dose interruptions due to adverse events[b]	16 (25)	15 (23)	8 (13)	10 (16)
Mean relative dose intensity, % (SD)	91.2 (13.01)	90.7 (14.36)	96.1 (10.34)	94.8 (10.48)

[a]Delay ≥4 days in starting the next cycle.
[b]Includes reason 'adverse events and other'.
[c]Missed doses in the middle of a cycle.
SD, standard deviation.

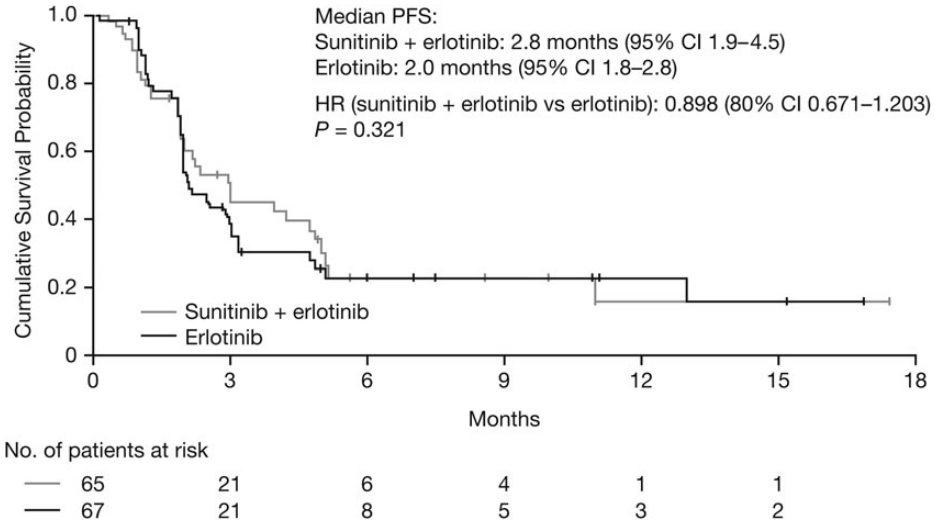
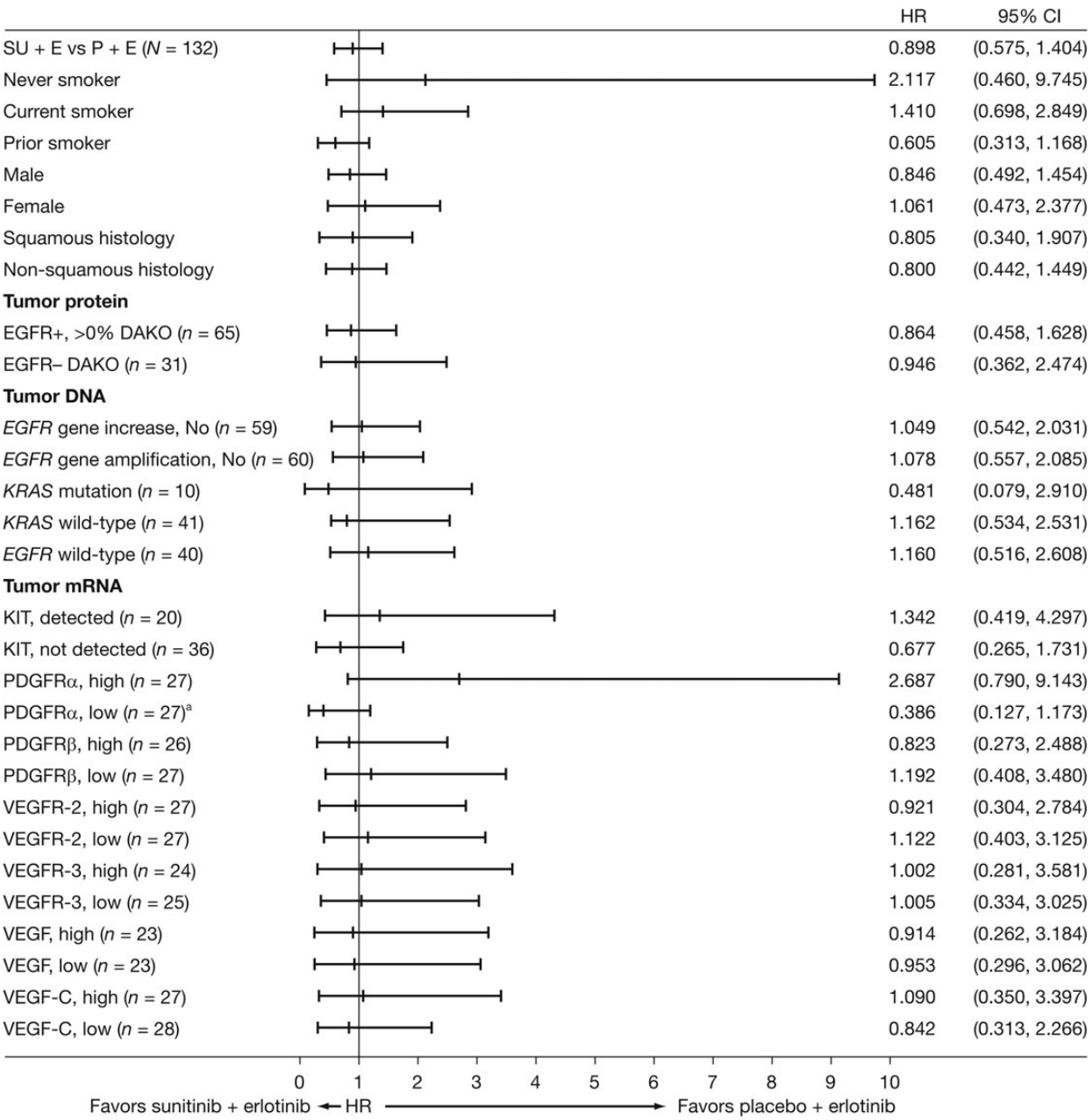


Figure 2. Kaplan–Meier estimates of progression-free survival (PFS).

Table 3. Treatment-related AEs experienced by ≥10% of patients in either treatment arm

	Sunitinib + erlotinib ($n = 64$)[a]			Placebo + erlotinib ($n = 64$)		
Adverse event, *n* (%)	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Diarrhea	35 (55)	11 (17)	0	21 (33)	1 (2)	0
Rash	26 (41)	5 (8)	0	19 (30)	2 (3)	0
Fatigue	20 (31)	6 (9)	0	16 (25)	2 (3)	0
Decreased appetite	19 (30)	3 (5)	0	8 (13)	0	0
Dry skin	18 (28)	0	0	15 (23)	0	0
Nausea	18 (28)	3 (5)	0	9 (14)	0	0
Dysgeusia	12 (19)	0	0	6 (9)	0	0
Mucosal inflammation	11 (17)	1 (2)	0	6 (9)	0	0
Vomiting	10 (16)	0	0	7 (11)	1 (2)	0
Thrombocytopenia	8 (13)	3 (5)	1 (2)	0	0	0
Pruritus	7 (11)	0	0	14 (22)	0	0
Acne	7 (11)	0	0	8 (13)	0	0
Dermatitis acneiform	6 (9)	0	0	11 (17)	0	0
Exfoliative rash	3 (5)	0	0	7 (11)	0	0

[a]A grade 5 intracranial hemorrhage was reported in one patient 31 days post dose (erlotinib and sunitinib). It was not considered an on-study event because it occurred after the 28-day post-treatment window; however, it was considered related to both erlotinib and sunitinib.



[a]$P = 0.040$ (1-sided log-rank).
E, erlotinib; P, placebo; SU, sunitinib.
EGFR immunohistochemistry: DAKO positivity defined as >0% of tumor cells demonstrating membranous staining for EGFR. A similar correlation was observed with EGFR immunohistochemistry analyzed according to BR21 methodology (>10% of tumor cells demonstrating membranous staining for EGFR; data not shown).[28]

Figure 3. Subgroup analyses of progression-free survival (PFS).

the second-line setting did not prolong OS or PFS in the phase III BeTa Lung trial, despite promising results in two phase II trials [31–33]. These trials indicate the difficulties of identifying novel, effective treatment combinations for unselected patients with refractory NSCLC.

Improving clinical outcomes in patients with recurrent NSCLC remains challenging. This study showed no difference between the treatment arms in PFS or OS in such patients. Some individuals may benefit from angiogenesis inhibition plus EGFR inhibition, but advances in molecular markers will be needed to identify the likely responders to this and other targeted combinations.

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disclosure

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