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ORIGINAL REPORT

Randomized Phase II Study of Dacomitinib (PF-00299804), an Irreversible Pan–Human Epidermal Growth Factor Receptor Inhibitor, Versus Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer

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See accompanying editorial on page 3322 and articles on pages 3330 and 3417

A B S T R A C T

Purpose
This randomized, open-label trial compared dacomitinib (PF-00299804), an irreversible inhibitor of human epidermal growth factor receptors (EGFR)/HER1, HER2, and HER4, with erlotinib, a reversible EGFR inhibitor, in patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Patients with NSCLC, Eastern Cooperative Oncology Group performance status 0 to 2, no prior HER-directed therapy, and one/two prior chemotherapy regimens received dacomitinib 45 mg or erlotinib 150 mg once daily.

Results
One hundred eighty-eight patients were randomly assigned. Treatment arms were balanced for most clinical and molecular characteristics. Median progression-free survival (PFS; primary end point) was 2.86 months for patients treated with dacomitinib and 1.91 months for patients treated with erlotinib (hazard ratio [HR] = 0.66; 95% CI, 0.47 to 0.91; two-sided $P = .012$); in patients with *KRAS* wild-type tumors, median PFS was 3.71 months for patients treated with dacomitinib and 1.91 months for patients treated with erlotinib (HR = 0.55; 95% CI, 0.35 to 0.85; two-sided $P = .006$); and in patients with *KRAS* wild-type/*EGFR* wild-type tumors, median PFS was 2.21 months for patients treated with dacomitinib and 1.84 months for patients treated with erlotinib (HR = 0.61; 95% CI, 0.37 to 0.99; two-sided $P = .043$). Median overall survival was 9.53 months for patients treated with dacomitinib and 7.44 months for patients treated with erlotinib (HR = 0.80; 95% CI, 0.56 to 1.13; two-sided $P = .205$). Adverse event-related discontinuations were uncommon in both arms. Common treatment-related adverse events were dermatologic and gastrointestinal, predominantly grade 1 to 2, and more frequent with dacomitinib.

Conclusion
Dacomitinib demonstrated significantly improved PFS versus erlotinib, with acceptable toxicity. PFS benefit was observed in most clinical and molecular subsets, notably *KRAS* wild-type/*EGFR* any status, *KRAS* wild-type/*EGFR* wild-type, and *EGFR* mutants.

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INTRODUCTION

Erlotinib and gefitinib are proven therapies for treatment of advanced non–small-cell lung cancer (NSCLC).[1,2] These reversible tyrosine kinase inhibitors (TKIs) selectively target HER1 (human epidermal growth factor receptor [EGFR, ErbB1]), one of the four HER family receptors (EGFR, ErbB1, HER2/*neu* [ErbB2], HER3 [ErbB3], HER4 [ErbB4]) and are particularly effective in the first-line treatment of NSCLC harboring *EGFR*-sensitizing mutations known to be common oncogenic drivers in NSCLC.[3-5] EGFR/HER ligand binding induces homo- and heteroreceptor dimerization, enabling downstream signaling that initiates several cellular processes including growth, proliferation, differentiation, and migration.[6,7]

Agents targeting a single member of the HER family, such as erlotinib and gefitinib, inhibit signaling through competitive, reversible binding at the

EGFR/HER1 tyrosine kinase domain. In contrast, dacomitinib (PF-00299804), a pan-HER inhibitor, irreversibly (covalently) binds to the adenosine triphosphate domain of each of the three kinase-active members of the HER family: EGFR/HER1, HER2, and HER4.[8,9] In preclinical studies, relative to erlotinib and gefitinib, dacomitinib demonstrated higher potency HER kinase inhibition and greater anticancer activity in gefitinib- and erlotinib-sensitive and -resistant cell line and xenograft NSCLC models.[8,9] In patients with progressive NSCLC after treatment with an EGFR TKI and one or more chemotherapy regimens, dacomitinib showed antitumor activity in phase I and II trials, suggesting potential utility in earlier lines of therapy.[10-12] On the basis of these data, we conducted a phase II randomized study (www.clinicaltrials.gov; NCT 007 69067) comparing dacomitinib with erlotinib as second-/third-line treatment for patients with advanced NSCLC.

PATIENTS AND METHODS

Patient Population

Patients aged ≥ 18 years with histologically confirmed advanced NSCLC and documented histologic subtype were eligible. Additional key inclusion criteria were disease progression after one or two prior chemotherapy regimens for advanced disease, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST),[13] fresh or archival tumor tissue availability at baseline for molecular testing, adequate organ function, and resolution to grade 1/baseline of acute toxicities from prior therapy ≤ 2 weeks before randomization. Exclusion criteria included prior EGFR-targeted therapy, known leptomeningeal or symptomatic brain metastases, clinically significant gastrointestinal abnormalities, interstitial lung disease, or uncontrolled cardiovascular disease. Patients were also excluded if they had evidence of an additional malignancy or concurrent treatment (within 7 days before initiation to end of trial treatment) with inhibitors/inducers of CYP3A4 if randomly assigned to erlotinib or drugs with a narrow therapeutic index if highly dependent on CYP2D6 metabolism if randomly assigned to dacomitinib (see Appendix, online only, for additional details).

Trial Design and Treatment

This global, multicenter, randomized, open-label, active comparator phase II trial compared the primary end point, progression-free survival (PFS), between dacomitinib and erlotinib. Secondary end points included best overall response rate (RR), duration of response (DR), overall survival (OS), safety, and patient-reported outcomes (PRO) of health-related quality of life (HRQoL) and disease-/treatment-related symptoms. Exploratory end points included determination of *EGFR* and *KRAS* mutations in tumor tissue and evaluation of dacomitinib trough concentrations after repeated dosing.

Patients were randomly assigned (1:1) to receive oral erlotinib (150 mg once daily) or oral dacomitinib (45 mg once daily) with stratification by known key prognostic factors for benefit from EGFR TKI: smoking status (non *v* ever smoker), race (Asian *v* non-Asian), and histologic subtype of NSCLC (adenocarcinoma *v* nonadenocarcinoma). Patients were assessed in 28-day cycles. Up to two dose reductions for toxicity were permitted; dose re-escalation was not permitted. Treatment was discontinued for disease progression, intolerance, patient withdrawal, or death (see Appendix for additional details). Subsequent treatment was at the investigator's discretion; cross-over from erlotinib to dacomitinib was prohibited. Suggested measures for managing dermatologic toxicity included topical corticosteroids or antibiotics for grade 1 adverse events (AEs) and oral antibiotics for grades worse than 1. Antidiarrheal medication was optional for treating grade 1 toxicity but recommended for grades worse than 1.

This trial was conducted in compliance with the International Conference on Harmonization Good Clinical Practice Guidelines protocol and with approval from an independent ethics committee. All patients provided written, informed consent before study enrollment.

Evaluation of Antitumor Activity

Antitumor activity was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) scans using RECIST version 1.0. Tumor assessments were performed at baseline, at the end of cycles 2 to 6, and every other cycle thereafter. Clinical benefit data (PFS, RR, and DR) were reported per investigators' assessment.

Evaluation of Safety and Tolerability

Safety and tolerability were assessed during the trial (from initiation of study treatment until at least 28 days after the last dose of study drug) by standard monitoring/methods (see Appendix for additional details).

Pharmacokinetic Analyses

At selected study sites, blood samples were collected from patients receiving dacomitinib, predose, on day 1 of cycles 1 through 4, and between days 10 and 14 of cycle 1. Concentration-time data were calculated for dacomitinib and its metabolite, PF-05199265.

PROs

PROs were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module, its lung cancer module, and the Dermatology Life Quality Index. Additional details of the instruments used are available (see Appendix). Patients completed self-administered questionnaires predose, at baseline (day 1, cycle 1), between days 10 and 14 of cycle 1, on day 1 of each subsequent cycle, and at the end of treatment.

Statistical Rationale for Study Design and Statistical Analyses

Enrollment of at least 160 patients (80 per treatment arm) with a minimum of 128 PFS events was required to detect a ≥ 45% improvement in PFS with dacomitinib over erlotinib, with at least 80% power and a one-sided significance level of 0.10 using a log-rank test. Stratified log-rank analyses were conducted to mitigate imbalances in key prognostic factors for benefit from HER-directed therapy in NSCLC (*EGFR* mutation, *KRAS* mutation, and baseline ECOG PS). All efficacy end points were analyzed in the intent-to-treat population; safety analyses were conducted in the as-treated population. Dacomitinib concentration-time data were summarized by descriptive statistics.

RESULTS

Patient Characteristics and Disposition

Between November 2008 and October 2009, 188 patients were randomly assigned to dacomitinib (n = 94) or erlotinib (n = 94; Fig 1). Patient baseline characteristics were balanced between treatment arms, except for baseline ECOG PS 2 (dacomitinib, n = 19; erlotinib, n = 3), *EGFR* mutation (*EGFR*: dacomitinib, n = 19; erlotinib, n = 11), and number of patients receiving two prior chemotherapy regimens (dacomitinib, n = 40; erlotinib, n = 27; Table 1). The overall rate of determination of mutation status was 80% and 81% for *KRAS* and *EGFR*, respectively. All patients were followed up for PFS and OS, with only five patients lost to follow-up.

Efficacy

PFS was analyzed when 167 events had occurred and six patients, all receiving dacomitinib, remained on study treatment. Overall, the estimated median PFS was 2.86 months for dacomitinib and 1.91 months for erlotinib, with a hazard ratio (HR) of 0.66, 95% CI, 0.47 to 0.91, and two-sided $P = .012$ based on a stratified log-rank test with *EGFR* mutation status, *KRAS* mutation status, and baseline ECOG PS as stratification factors (Fig 2A). The overall improvement in PFS seen with dacomitinib was noted across most clinical and molecular subsets assessed (Fig 2B), including patients with tumors confirmed as *KRAS* wild-type/*EGFR* any status (including mutant; median PFS, 3.71 months for dacomitinib, 1.91 months for erlotinib; HR = 0.55; 95% CI, 0.35 to 0.85; two-sided $P = .006$; Appendix Fig A1A, online

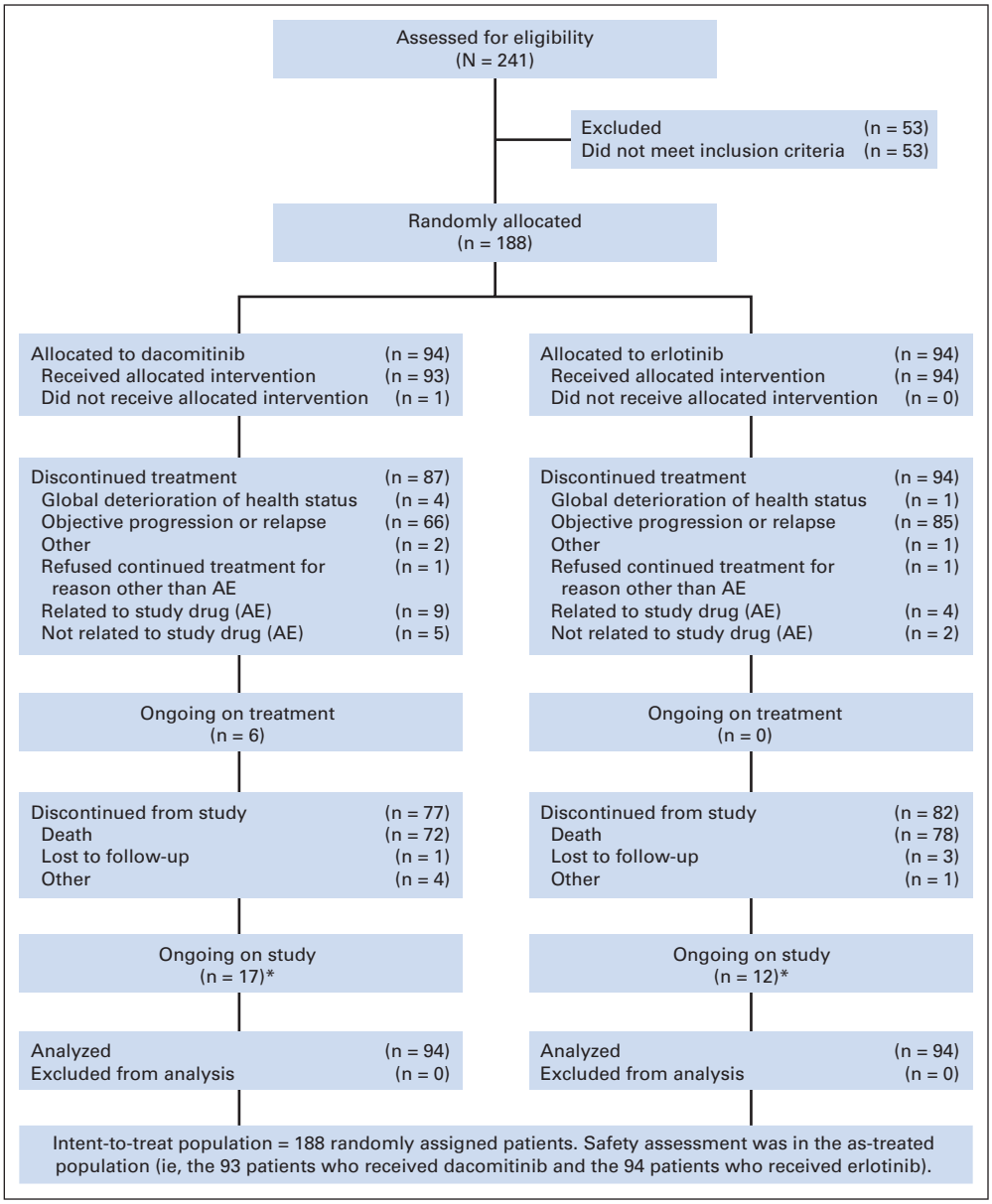

Fig 1. CONSORT diagram showing treatment assignment and patient disposition. (*) "Ongoing on study" refers to those patients who are either still receiving study treatment or are in the post-treatment follow-up period for adverse events (AEs), if any, and overall survival.

only), *KRAS* wild-type/*EGFR* wild-type (median PFS, 2.21 months for dacomitinib, 1.84 months for erlotinib; HR = 0.61; 95% CI, 0.37 to 0.99; two-sided $P = .043$; Appendix Fig A1B, online only). For the *EGFR* mutant subset, median PFS was 7.44 months for both dacomitinib and erlotinib (HR = 0.46; 95% CI, 0.18 to 1.18; two-sided $P = .098$; Appendix Fig A1C, online only).

The objective response rate (ORR) for dacomitinib was 17.0%, with one complete response, and 5.3% for erlotinib (two-sided $P = .011$). The clinical benefit response rate (complete response plus partial response plus stable disease ≥ 24 weeks) was also significantly greater for dacomitinib than for erlotinib (29.8% *v* 14.9%, respectively; two-sided $P = .014$). The median duration of response was 16.56 months (range, 3.15 to 23.95+) for dacomitinib and 9.23 months (range, 5.69 to 16.58) for erlotinib, respectively.

OS was analyzed after 150 deaths (80%) had occurred (72 patients receiving dacomitinib and 78 patients receiving erlotinib). A numerical trend toward favorable OS with dacomitinib was noted, but did not reach statistical significance (median OS, 9.53 months for dacomitinib *v* 7.44 months for erlotinib; HR = 0.80, 95% CI, 0.56 to 1.13, and two-sided $P = .205$ based on a stratified log-rank test with *EGFR* mutation status, *KRAS* mutation status, and baseline ECOG PS as stratification factors; Appendix Fig A2, online only).

Subsequent Therapy After Discontinuation From Study Treatment

After discontinuation, 84 patients (46%) overall received subsequent therapy, more among patients receiving erlotinib (47 of 94, 50%) than patients receiving dacomitinib (37 of 88, 42%). After discontinuation from the study, an EGFR TKI was given to three patients previously being treated with erlotinib and 11 previously being treated with dacomitinib (Appendix Table A1, online only).

Table 1. Patient Baseline Characteristics (N = 188)

Characteristic	Dacomitinib 45 mg Once Daily (n = 94) No.	%	Erlotinib 150 mg Once Daily (n = 94) No.	%
Age, years				
Median	60.0		62.0	
Range	24-82		27-85	
Sex				
Male	55		56	
Female	39		38	
Race				
White	68	72.3	67	71.3
Asian	23	24.5	24	25.5
Other	3	3.2	3	3.2
Smoking status				
Nonsmoker[a]	18	19.1	19	20.2
Ever-smoker[b]	76	80.9	75	79.8
Histology				
Adenocarcinoma	62	66.0	61	64.9
Nonadenocarcinoma	32[c]	34.0	33[c]	35.1
ECOG PS				
0	29	30.9	29	30.9
1	46	48.9	62	66.0
2	19	20.2	3	3.2
No. of prior lines of chemotherapy				
1	51	54.3	63	67.0
2	40	42.6	27	28.7
3[d]	3	3.2	4	4.3
KRAS mutational status				
Wild type	57	60.6	64	68.1
Mutant	17	18.0	14	14.9
Unknown	20	21.3	16	17.0
EGFR mutation status				
Wild type	58	61.7	65	69.1
Mutant	19	20.2	11	11.7
Unknown	17	18.1	18	19.1
Mean baseline QLQ-C30 score, diarrhea	9.36[e]		7.58[f]	
Mean baseline QLQ-LC13 score, sore mouth	6.37[e]		3.41[f]	
Mean baseline DLQI scores				
Symptoms and feelings	0.56[g]		0.32[h]	
Total score	0.88[g]		0.71[i]	

Abbreviations: DLQI, Dermatology Life Quality Index; ECOG PS, Eastern Cooperative Oncology Group performance status; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30; QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire lung cancer module.

[a]< 100 cigarettes/cigars/pipes over lifetime.

[b]> 100 cigarettes/cigars/pipes over lifetime.

[c]Squamous, n = 23.

[d]Patients receiving a third prior chemotherapy regimen were treated in the adjuvant setting or with combined chemotherapy plus radiotherapy for localized disease at diagnosis.

[e]n = 89.

[f]n = 88.

[g]n = 91.

[h]n = 87.

[i]n = 86.

Safety and Tolerability

Frequently reported AEs included diarrhea, acneiform dermatitis, stomatitis, mucosal inflammation, and paronychia; the majority of events were of grade 1 or 2 severity and manageable with standard supportive care (Table 2). Grade 4 AEs comprised anemia, elevation of ALT, AST, and increased serum creatinine experienced by a single patient on dacomitinib; and pneumonia, in one patient on erlotinib. Four treatment-related deaths occurred during the study. Deaths were due to pneumonia and pneumonitis (one patient each) on dacomitinib, and pneumonia and pulmonary embolism (one patient each) on erlotinib. Of the two treatment-related deaths on dacomitinib, one patient with a history of partial pneumonectomy and chronic obstructive pulmonary disease was hospitalized for dyspnea and leukocytosis. This patient died of pneumonia considered by the investigator to be possibly related to dacomitinib. The second patient experienced fever, cough, and hemoptysis, had concurrent progression of NSCLC, and changes on radiologic imaging described as pneumonitis that were considered by the investigator to be possibly related to dacomitinib.

Adverse events necessitating treatment withdrawal were uncommon in both treatment arms. Seven patients discontinued in the dacomitinib arm, five with grade 1 to 3 dermatologic skin toxicity (including four during the first month of treatment), one with grade 2 diarrhea, and one with grade 3 dehydration. Two patients discontinued in the erlotinib group, one with grade 2 nausea and one with grade 2 malaise (Table 3).

Treatment-related dose reductions were required by 38 patients receiving dacomitinib (40.9% total: 31.2% with one, 7.5% with two, 2.2% with three dose reductions) and 16 patients receiving erlotinib (17%: all with one reduction). Hematologic and biochemical assessments did not reveal any clinically relevant changes (data not shown). No clinically relevant decreases of left ventricular ejection fraction related to study drug were reported for either treatment.

PROs

Dacomitinib resulted in clinically meaningful improvements (> minimal important difference of 10 points) in cough, dyspnea, chest pain, arm/shoulder pain, fatigue, and physical function relative to erlotinib at various time points (data not shown; preliminary data have been previously reported and final results will be reported in full subsequently).[14] There was an increase in patient-reported scores, indicating higher levels of symptoms, for the treatment-related AEs of diarrhea, mucositis (sore mouth), and skin toxicity that peaked early in treatment and stabilized over time in both treatment arms (Fig 3). Wherein the score 0 = no symptoms and 100 = most symptoms, patients on both arms reported scores that were below the midpoint at their worst: the score for diarrhea for dacomitinib was 48.15 (cycle 2, day 1) and for erlotinib was 31.15 (cycle 3, day 1). For skin toxicity, the Dermatology Life Quality Index mean total score was highest at cycle 4, day 1 (5.95), for dacomitinib and at cycle 2, day 1 (5.16), for erlotinib (Fig 3); qualitatively, scores for both groups indicated that skin toxicity had a small effect on patient's life during the previous week.

Pharmacokinetics

Dacomitinib pharmacokinetic exposures (C_{trough}) were consistent with those previously reported after 45-mg daily dosing through multiple cycles (Appendix Fig A3, online only).[10,11,15] PF-05199265, the major circulating metabolite of dacomitinib that has shown in vitro activity as a pan-HER inhibitor, was present at steady-state at

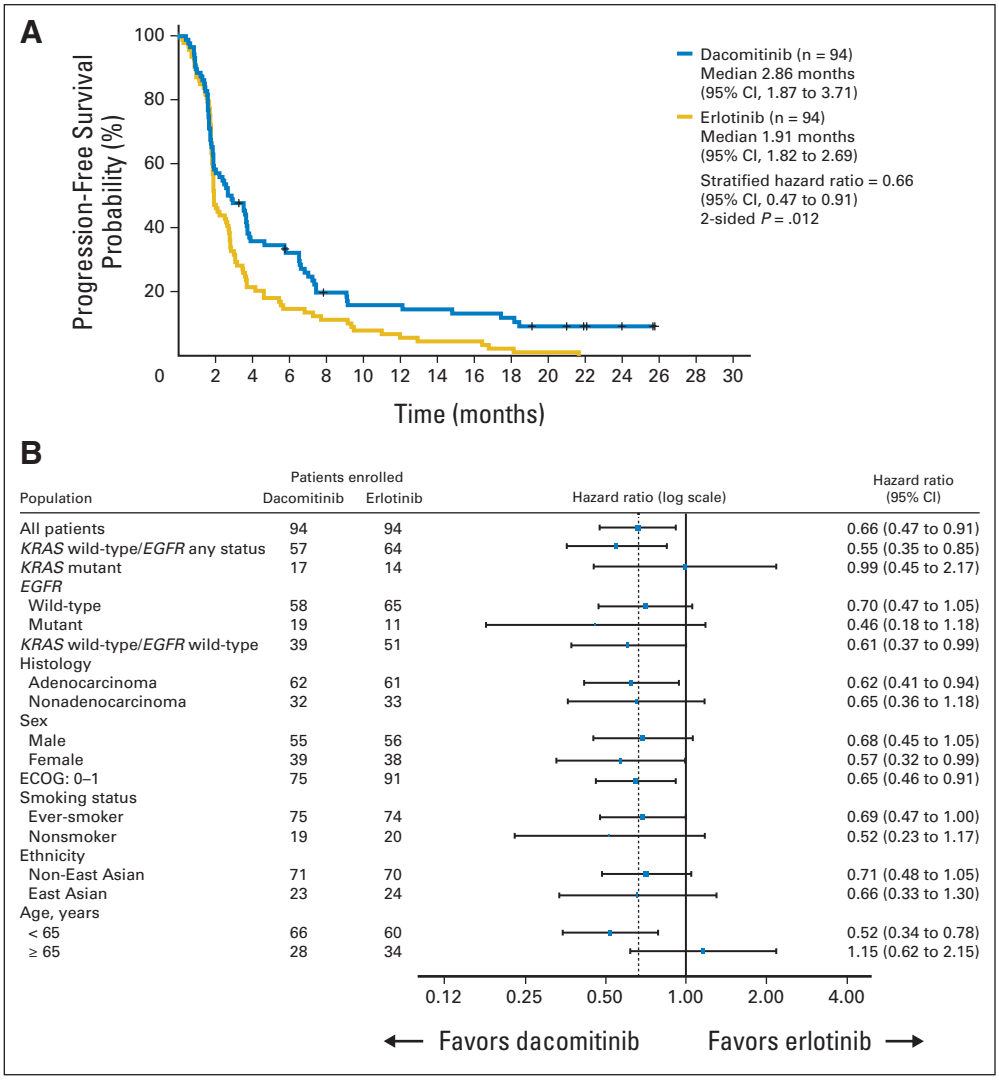

Fig 2. (A) Kaplan-Meier plot of progression-free survival for all patients and (B) Forest plot for the subgroup analyses of progression-free survival. ECOG, Eastern Cooperative Oncology Group.

concentrations approximately 10% of the parent compound; concentrations of the metabolite were consistent over the time period assessed (cycles1 through 4).

DISCUSSION

This trial, which is the first to directly compare an irreversible pan-HER TKI with a reversible EGFR selective TKI, demonstrated improved PFS after treatment with dacomitinib (primary end point) over treatment with erlotinib (HR = 0.66, two-sided $P = .012$). It is possible that this result from the overall study population was driven by the observed imbalance in the number of patients whose tumors harbored known *EGFR*-sensitizing mutations (20% *v* 12% for dacomitinib and erlotinib, respectively), differences in the number of patients with *KRAS* wild-type/*EGFR* any status tumors (61% *v* 68%), and the imbalance in baseline ECOG PS (20% *v* 3%). However, the stratified log-rank test addressed the likelihood of the null hypothesis of equality of HRs across strata.[16] Significant results from the stratified log-rank test coupled with the significant unadjusted HR for the overall population (HR = 0.66, two-sided $P = .009$) strongly favor superiority for dacomitinib over erlotinib in PFS. In addition, the consistent distribution of subgroup results around the overall HR suggests the reliability of the unadjusted HR and supports the differential efficacy observed for dacomitinib over erlotinib. Furthermore, subset analysis of PFS in patients whose tumors were *KRAS* wild-type/*EGFR* wild-type revealed additional PFS benefit with dacomitinib. These analyses suggest that the imbalance in patients with *EGFR* mutations in the overall population was not the sole driver of the benefit observed. Furthermore, these results raise the possibility that patients with *KRAS* wild-type/*EGFR* any status NSCLC may particularly benefit from dacomitinib. Interpretation of subgroup analyses should, however, be approached with caution, as subgroups may not be balanced with respect to other key prognostic factors for PFS and OS in NSCLC or for yet to be identified factors predictive of response to HER-directed therapy.

KRAS is a downstream effector of *EGFR* signal transduction, and tumors with constitutively active *KRAS* might reasonably be expected to be resistant to *EGFR* inhibition.[17] Prior studies have noted *KRAS* mutation as a negative predictor of response to EGFR TKIs, although the significance of *KRAS* mutations in predicting clinical benefit to

Table 2. Most Frequent Treatment-Related Adverse Events Occurring in ≥ 10% of Patients in Each Treatment Arm

	Dacomitinib 45 mg Once Daily (n = 93)								Erlotinib 150 mg Once Daily (n = 94)							
	Grade 1		Grade 2		Grade 3*		Total		Grade 1		Grade 2		Grade 3†		Total	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Diarrhea	30	32.3	27	29.0	11	11.8	68	73.1	35	37.2	6	6.4	4	4.3	45	47.9
Dermatitis acneiform	30	32.3	20	21.5	10	10.8	60	64.5	26	27.7	22	23.4	6	6.4	54	57.4
Stomatitis	14	15.1	12	12.9	1	1.1	27	29.0	5	5.3	4	4.3	1	1.1	10	10.6
Decreased appetite	16	17.2	7	7.5	1	1.1	24	25.8	10	10.6	11	11.7	0		21	22.3
Paronychia	11	11.8	10	10.8	3	3.2	24	25.8	5	5.3	2	2.1	1	1.1	8	8.5
Mucosal inflammation	11	11.8	10	10.8	2	2.2	23	24.7	2	2.1	4	4.3	0		6	6.4
Dry skin	15	16.1	6	6.5	1	1.1	22	23.7	9	9.6	3	3.2	2	2.1	14	14.9
Exfoliative rash	6	6.5	8	8.6	2	2.2	16	17.2	6	6.4	7	7.4	1	1.1	14	14.9
Nausea	11	11.8	3	3.2	2	2.2	16	17.2	11	11.7	3	3.2	1	1.1	15	16.0
Fatigue	9	9.7	5	5.4	1	1.1	15	16.1	13	13.8	6	6.4	1	1.1	20	21.3
Pruritus	9	9.7	5	5.4	0	0.0	14	15.1	12	12.8	3	3.2	0	0.0	15	16.0
Acne	5	5.4	5	5.4	2	2.2	12	12.9	6	6.4	5	5.3	0	0.0	11	11.7
Weight decreased	7	7.5	4	4.3	0	0.0	11	11.8	6	6.4	3	3.2	0	0.0	9	9.6
Erythema multiforme	5	5.4	4	4.3	1	1.1	10	10.8	3	3.2	1	1.1	0	0.0	4	4.3
Hand-foot syndrome	4	4.3	6	6.5	0	0.0	10	10.8	3	3.2	2	2.1	0	0.0	5	5.3

NOTE. Adverse events graded according to National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0.1.
*Four grade 4 adverse events were considered to be related to dacomitinib (anemia, increased alanine aminotransferase, increased aspartate aminotransferase, and increased blood creatinine; all in a single patient).
†One grade 4 adverse event (pneumonia) considered to be related to erlotinib was reported.

anti-EGFR therapies, as measured by PFS and OS, remains unclear.[18] This lack of clarity may reflect the retrospective nature of the published studies and the small sample sizes available. In the present trial, patients with *KRAS* wild-type/*EGFR* any status tumors treated with dacomitinib had a two-fold improvement in PFS over erlotinib. The stratified log-rank test resulted in an HR of 0.55 (two-sided $P = .006$), consistent with the conclusion that imbalance between treatment arms in numbers of patients with *EGFR* mutant tumors was not solely responsible for the benefit observed with dacomitinib. Given the degree of benefit reported here for patients with *KRAS* wild-type/*EGFR* any status or *KRAS* wild-type/*EGFR* wild-type tumors, and the uncertainty surrounding KRAS as a predictor of response in NSCLC, there is clearly a need for prospective studies of the role of *KRAS* in tumor response to pan-HER inhibition.

A trend toward improved OS with dacomitinib relative to erlotinib was observed that did not reach statistical significance. For most clinical and molecular subsets, PFS and OS benefit were directionally similar, although data are not mature for some subsets, with seven patients remaining on treatment with dacomitinib. The lack of statistical significance may be due to the trial lacking sufficient power to address OS, or due to the imbalance in the number of patients who received poststudy therapy—known to be an important confounding variable for OS.[19] A subanalysis of OS showed that patients who received subsequent therapy had improved survival relative to those who did not (stratified log-rank analysis: HR = 0.67, 95% CI, 0.38 to 1.16, two-sided $P = .145$ for dacomitinib; and HR = 0.35, 95% CI, 0.22 to 0.57, two-sided $P < .001$) for erlotinib).

Consistent with the expected toxicities of EGFR TKIs, skin effects and diarrhea were prominent AEs.[20-22] Such events were more common with dacomitinib than with erlotinib, but the majority were mild or moderate in severity and manageable, with relatively few patients discontinuing on either arm as a result of AEs. It is becoming widely accepted that, in addition to conventional efficacy outcomes such as PFS and OS, quality of life (from the patients' perspective) is an important component of high-quality cancer care.[23] Although diarrhea, mucositis, and skin toxicity were more common with dacomitinib than with erlotinib, these AEs were tolerable—as supported by discontinuation rates, dose reduction rates, and mean PRO scores between arms—and improved over time.

It is possible that the improvements in PFS and other end points seen with dacomitinib relative to erlotinib in this study reflect the mechanism of action of dacomitinib as determined in preclinical studies, which potentially includes more complete inhibition of HER signaling by receptor homo- and heterodimerization through targeting of all three kinase-active HER receptors and permanent blockade of signaling by covalent receptor modification.[8,9,24] In addition, prolonged drug exposure due to pharmacologic characteristics may play a role, as may other unknown factors.[8] Dacomitinib and the pan-HER EGFR TKI, afatinib, are currently in phase III studies in different NSCLC settings. In the

Table 3. Permanent Discontinuations Arising From Treatment-Related Adverse Events

	Adverse Event (day of onset)		
Agent	Grade 1	Grade 2	Grade 3
Dacomitinib	Exfoliative rash, hand-foot syndrome, both in one patient (day 29)	Skin infection (day 99), diarrhea (day 99)	Skin fissures (day 29), dehydration (day 28), dermatitis acneiform (day 17), rash: acneiform and erythematous (day 7)*
Erlotinib		Nausea (day 15), malaise (day 48)	

*This patient also had grade 2 pain and grade 2 pruritus onset at day 7.

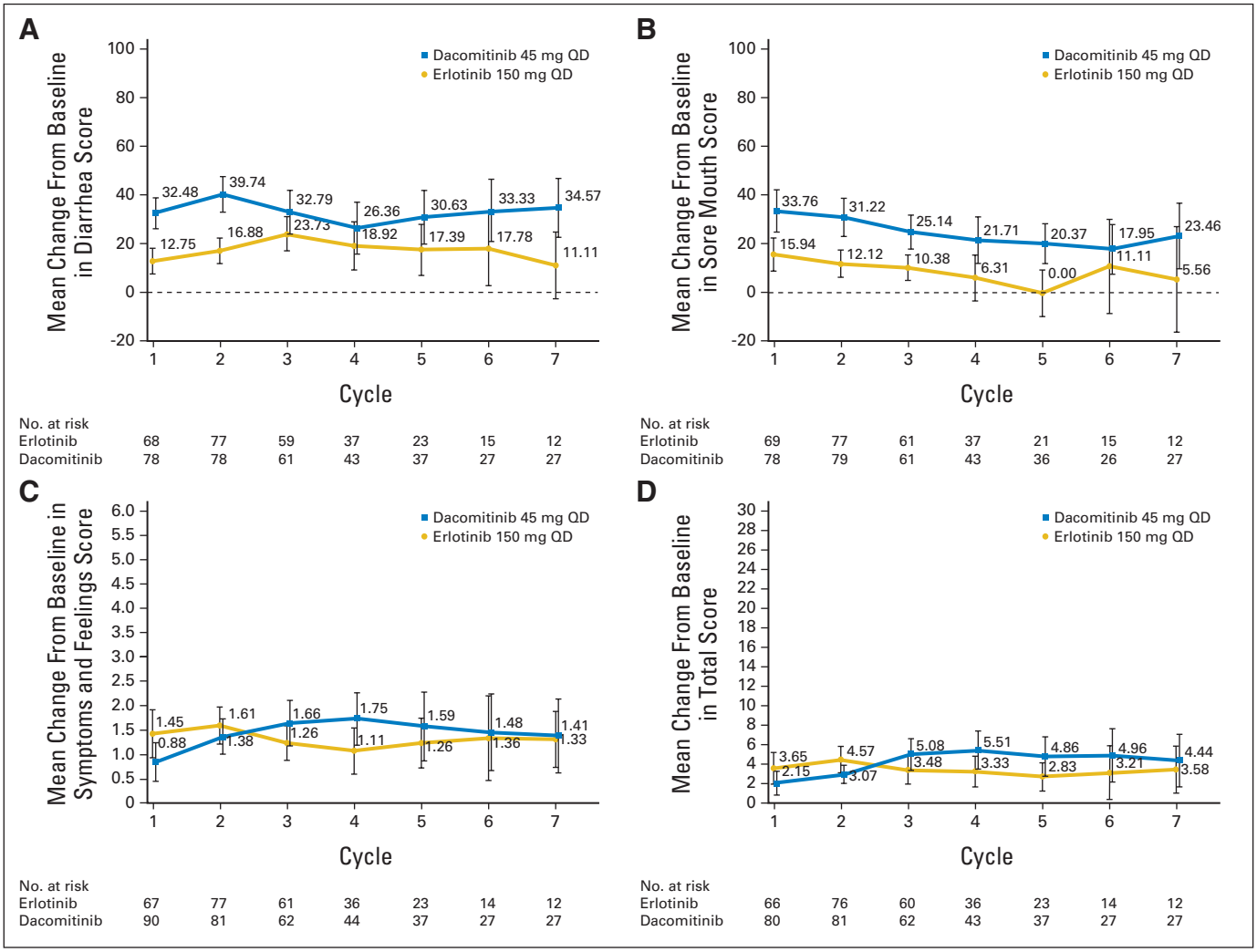

Fig 3. Patient-reported outcomes for treatment-related adverse effects; mean change from baseline in (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30: diarrhea, (B) EORTC QLQ lung module: sore mouth, (C) Dermatology Life Quality Index (DLQI) symptoms and feelings, and (D) DLQI total score. Higher scores indicate higher levels of symptoms or a higher degree of impairment of functioning; lower scores indicate fewer symptoms or a lower degree of impairment of functioning. Cycle 1 refers to cycle 1 days 10 to 14. Numbers below figures are n per cycle for each arm. EORTC scales are scored 0 to 100; DLQI total scores range from 0 to 30, and the DLQI subscale symptoms and feelings is scored 0 to 6. QD, once daily.

LUX Lung-1 phase II/III study, conducted in patients previously treated with chemotherapy and a prior EGFR TKI, afatinib was associated with a safety profile consistent with EGFR-directed agents and showed a clear PFS benefit versus placebo, although survival was not superior. The results documented here for dacomitinib suggest that irreversible pan-HER inhibition may offer a new treatment option for patients with advanced NSCLC, potentially representing an effective alternative to reversible inhibition of EGFR.

A phase III study (ARCHER 1009 [Advanced Research for Cancer Targeted Pan-HER Therapy]) is underway to confirm the findings of the present study for second-/third-line therapy in patients with advanced NSCLC. This study includes coprimary end points (PFS in all patients and in patients with wild type *KRAS/EGFR* any status) to allow evaluation of dacomitinib in an unselected population and to prospectively evaluate the relationship between *KRAS* molecular status and clinical outcome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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