Original Article

A Phase 2 Trial of Dacomitinib (PF-00299804), an Oral, Irreversible Pan-HER (Human Epidermal Growth Factor Receptor) Inhibitor, in Patients With Advanced Non–Small Cell Lung Cancer After Failure of Prior Chemotherapy and Erlotinib

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BACKGROUND: This phase 2 trial (ClinicalTrials.gov identifier NCT00548093) assessed the efficacy, safety, and impact on health-related quality of life of dacomitinib (PF-00299804), an irreversible tyrosine kinase inhibitor (TKI) of human epidermal growth factor receptors (EGFR)/HER1, HER2, and HER4, in patients with *KRAS* wild-type non–small cell lung cancer (NSCLC). **METHODS:** Patients with advanced NSCLC, progression on 1 or 2 regimens of chemotherapy and erlotinib, *KRAS* wild-type or known *EGFR*-sensitizing mutant tumor, and Eastern Cooperative Oncology Group performance status of 0 to 2 received 45 mg of dacomitinib once daily continuously in 21-day cycles. **RESULTS:** A total of 66 patients enrolled (adenocarcinoma, n = 50; those without adenocarcinoma [nonadenocarcinoma], n = 16). The objective response rate (ORR) for patients with adenocarcinoma (primary endpoint) was 5% (2 partial responses; 1-sided $P = .372$ for null hypothesis [H_0]: ORR $\leq$ 5%) and 6% (1 partial response) for patients with nonadenocarcinoma. Responders included: 2 of 25 *EGFR* mutation-positive tumors; 1 of 3 *EGFR* wild-type with *HER2* amplification. Median progression-free survival was 12 weeks overall (n = 66) and 18 weeks (n = 26) for patients with *EGFR* mutation-positive tumors. Common treatment-related adverse events were of grade 1 or 2 severity, manageable with standard supportive care, and included diarrhea (grade 3 [G3], 12%), acneiform dermatitis (G3, 6%), exfoliative rash (G3, 3%), dry skin (G3, 0%), fatigue (G3, 3%), and stomatitis (G3, 2%). Six patients (9%) discontinued due to treatment-related adverse events. By patient report, NSCLC symptoms of dyspnea, cough, and pain (chest, arm/shoulder) showed improvement first observed after 3 weeks on therapy. **CONCLUSIONS:** Dacomitinib demonstrated preliminary activity and acceptable tolerability in heavily pretreated patients, and may offer benefit in molecularly defined patient subsets. ***Cancer*** **2014;120:1145–54.**

KEYWORDS: dacomitinib, PF-00299804, non–small cell lung cancer, erlotinib, adenocarcinoma, nonadenocarcinoma.

INTRODUCTION

Following failure of chemotherapy and erlotinib, treatment options are limited for patients with advanced non–small cell lung cancer (NSCLC). Reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib, selectively target EGFR/HER1, one of the members of the human epidermal growth factor receptor (HER) family, and are most effective in cancers harboring *EGFR* mutations. The remaining members of the HER family comprise HER2 and HER4 tyrosine kinases, and the kinase-null HER3.[1] HER family members act together via hetero- and homodimerization to enable downstream signaling pathways modulating a range of cellular activities, including growth, proliferation, differentiation, and migration.[1] In contrast to patients with *EGFR*-mutation-positive tumors,

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Additional Supporting Information may be found in the online version of this article.

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patients with *KRAS*-mutant NSCLC are unlikely to respond to gefitinib or erlotinib and do not have an improved progression-free survival (PFS) compared with those who have placebo following erlotinib therapy.[2]

Dacomitinib (PF-00299804) is a potent, irreversible, oral small-molecule inhibitor of HER1/EGFR, HER2, and HER4 tyrosine kinases with antitumor activity in both gefitinib-sensitive and gefitinib-resistant, including *EGFR T790M*, preclinical NSCLC models.[3,4] Dacomitinib demonstrated encouraging antitumor activity against NSCLC in Western and Japanese patients in phase 1 studies,[5,6] further supported by preliminary data from phase 2 NSCLC studies conducted in Asian patients with *KRAS* wild-type refractory disease[7]; unselected patients previously treated with chemotherapy[8]; and patients with *EGFR*-mutant disease (first-line treatment).[9] This phase 2 trial (ClinicalTrials.gov identifier NCT00548093) assessed the efficacy, safety, and impact on health-related quality of life (HRQoL) of dacomitinib in patients with *KRAS* wild-type NSCLC who progressed after 1 or 2 chemotherapy regimens and erlotinib.

MATERIALS AND METHODS

Patient Population

Main inclusion criteria were age $\geq$18 years, histologically or cytologically confirmed advanced NSCLC, progression on erlotinib and 1 or 2 regimens of chemotherapy, confirmation of *KRAS* wild-type tumor or known *EGFR* exon 19 deletion or *EGFR* exon 21 mutation (previously documented *EGFR* mutation was accepted when insufficient tissue was available for *KRAS* testing), and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2. Exclusion criteria included chemotherapy, radiotherapy, biological or investigational agents, or surgery within 4 weeks of study entry; EGFR inhibitors within 2 weeks of study entry; intolerance to erlotinib; prior investigational EGFR-targeted therapy without written agreement of the study sponsor; and uncontrolled or significant cardiovascular disease.

Trial Design and Treatment

This was a multicenter, open-label, phase 2 trial. To address differences in the expected response rates between tumors of different histologies,[10,11] 2 cohorts, comprising patients with adenocarcinoma and those without adenocarcinoma (nonadenocarcinoma), were enrolled. Patients received 45 mg of dacomitinib once daily on an empty stomach (2 hours before or after dacomitinib intake) on a continuous basis during a 21-day cycle. Dose interruptions of $<$2 weeks without discontinuation from the study were allowed for toxicity; 2 dose attenuation levels of 30 mg and then 20 mg were allowed. Treatment was discontinued for disease progression, intolerance (grade 3 or 4 toxicity or intolerable grade 2 toxicity that does not resolve to grade 1 or baseline after 2 weeks' interruption), global deterioration of health-related symptoms, protocol noncompliance, or patient withdrawal.

The primary endpoint was best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0[12] for patients with tumors of adenocarcinoma histology. Secondary efficacy endpoints included: BOR in patients with tumors of nonadenocarcinoma histology, duration of objective response, PFS, PFS at 6 months (PFS_{6M}), overall survival (OS), and OS at 6 (OS_{6M}) and 12 (OS_{12M}) months. Other secondary endpoints were safety; patient-reported outcomes (PROs) of HRQoL; disease- and treatment-related symptoms; pharmacokinetics (PK); pre- and posttreatment concentrations of the extracellular domains of HER2 and EGFR in serum; and genetic variation in *HER* family and *KRAS* genes from free tumor DNA in blood.

This trial was conducted in compliance with the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practice Guidelines protocol, and was approved by the Institutional Review Boards and/or Independent Ethics Committees at each of the participating investigational centers. All patients provided written, informed consent prior to study participation.

Evaluation of Antitumor Activity

Evaluation of antitumor activity per RECIST version 1.0[12] was by investigator review. Tumor assessments were performed at baseline and at the end of every even-numbered cycle or when progressive disease was suspected.

Evaluation of Safety and Tolerability

Safety and tolerability were assessed by standard methods from initiation of study treatment until $\geq$28 days after the last dose of study drug. Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Pharmacokinetic Analyses, Biomarker Determination, and Pharmacodynamic Analyses

Blood samples for PK analyses were collected up to 24 hours after dose on day 1 of cycle 1, before dose on days 2, 7, and 14 of cycle 1, and day 1 of cycle 2. PK parameters for dacomitinib, including the maximum concentration (C_{max}), the time to C_{max} (T_{max}), and the area under the plasma concentration curve from 0 to 24 hours ($AUC_{0\text{-}24}$), were analyzed using a noncompartmental

approach. Tumor tissue from new biopsies obtained at enrollment or archival samples (which may have been pre- or post-erlotinib) was analyzed for *EGFR* and *KRAS* gene mutation status using Qiagen Scorpion ARMS (Amplified Refractory Mutation System) allele-specific polymerase chain reaction assay; *HER2* mutation status was determined by DNA sequencing. *EGFR* and *HER2* gene amplification were assessed by fluorescence in situ hybridization. *EGFR* amplification was defined as >15 copies of *EGFR* gene signals in >10% of analyzed cells; *HER2* amplification was defined as a *HER2* gene/centromere of chromosome 17 ratio of >2. Blood samples for biomarker analysis were collected at baseline and prior to dosing on day 1 of each cycle. Concentrations of HER2 and EGFR extracellular domains were determined by enzyme-linked immunosorbent assay.

Patient-Reported Outcomes

PROs of HRQoL, disease symptoms specific to lung cancer, and side effects of treatment were assessed using the 30-question European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core module (EORTC QLQ-C30),[13] which includes functional, symptom, side effects, and global health status scales, and the 13-item Lung Cancer symptom-specific module (QLQ-LC13).[14] The impact of dacomitinib on patients' skin condition was assessed using the 10-item Dermatology Life Quality Index (DLQI) questionnaire.

Statistical Design and Analyses

The trial used a Fleming single-stage design for each patient population (adenocarcinoma and nonadenocarcinoma, respectively). The primary objective of this study was to test the null hypothesis (H_0) at the 0.05 significance level with 80% power that the objective response rate (ORR) in patients with adenocarcinoma did not exceed 5%. At the end of the study, if there were at least 6 objective responders in 44 response-evaluable patients, then the null hypothesis would be rejected, demonstrating that treatment with dacomitinib is associated with a true response rate that exceeds 5%. A secondary objective was to test the H_0 at the 0.05 significance level with 80% power that the ORR in patients with nonadenocarcinoma did not exceed 1%. At least 2 objective responders among 22 response-evaluable patients were required to reject the null hypothesis and conclude that treatment with dacomitinib demonstrates a true response rate that exceeds 1%.

Target enrollment of 49 and 25 patients with adenocarcinoma and nonadenocarcinoma, respectively, was required and accounted for a rate of nonevaluability for response of up to 10%. Baseline characteristics, PFS, PFS_{6M}, OS, OS_{6M}, and OS_{12M} were evaluated in the intent-to-treat population, safety in the as-treated population, and response was assessed in response-evaluable patients.

RESULTS

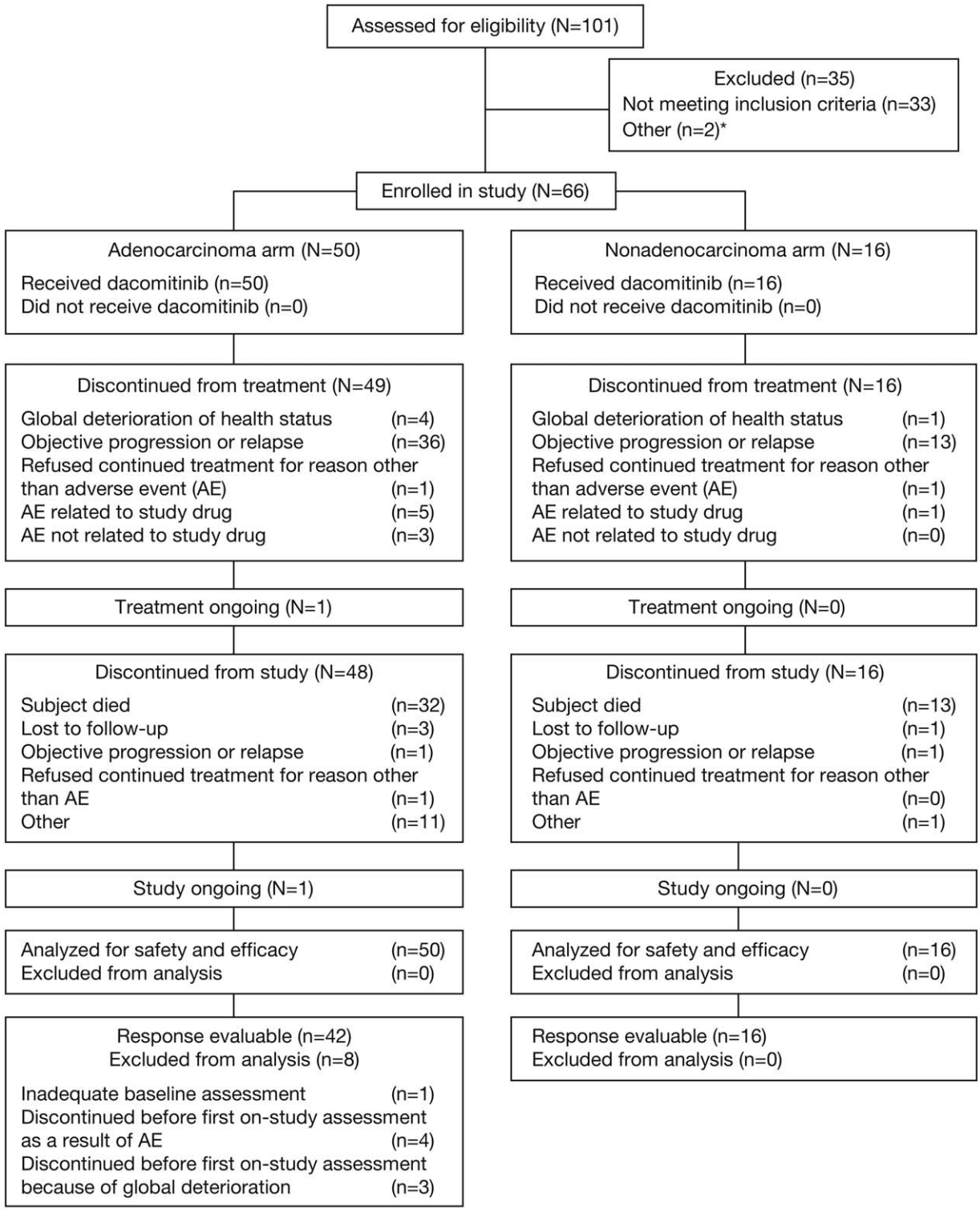
Patient Characteristics and Disposition

Sixty-six patients were enrolled between April 2008 and November 2009, 50 with adenocarcinoma and 16 with nonadenocarcinoma. Patient disposition is shown in Fig. 1. Enrollment of the nonadenocarcinoma arm was closed prior to reaching the planned target of 25 due to few nonadenocarcinoma patients identified with prior erlotinib treatment. Patient characteristics are summarized in Table 1. The majority of patients had received 2 or 3 prior treatment regimens (n = 26 [39%] each). In addition to erlotinib prior EGFR-directed therapies comprised gefitinib (n = 4), cetuximab (n = 3), and neratinib (n = 1). Fifty-five percent of the enrolled population were current or former smokers. Wild-type *KRAS* NSCLC was either directly confirmed (n = 54) or assumed from a known *EGFR* mutation (n = 12; *EGFR* mutation status was known for a total of 26 patients). Mutation and gene amplification data were collected from *EGFR* and *HER2* according to availability of sufficient tissue for analysis (Table 1). Six patients had *EGFR T790M* resistance mutation identified after treatment with erlotinib (Supporting Table 1; see online supporting information). *T790M* status was unknown in 54 patients who had biopsies taken prior to progression on erlotinib. Overall, 74% of patients started dacomitinib within 3 months of discontinuing erlotinib. Of the 26 patients who had *EGFR*-mutant tumors at baseline, the interval from discontinuing erlotinib to starting dacomitinib ranged from 15 to 544 days, with 69% starting dacomitinib within 3 months of discontinuing erlotinib.

Efficacy

Best Overall Response

In the overall population, the ORR for response-evaluable patients was 5.2% (3 partial responses [PRs] of durations 12, 24, and 66 weeks). The ORR for patients with adenocarcinoma was 4.8% (2 PRs; 1-sided $P = .372$). For patients with nonadenocarcinoma, the ORR was 6.3% (1 PR). The 25 response-evaluable patients with *EGFR* mutation-positive tumors (from both arms) achieved an ORR of 8% (2 PRs) and 17 (68%) achieved a BOR of stable disease (SD) ≥6 weeks (Table 2). Further details of the patients with PRs are presented in Supporting Table 2. Six patients had known *EGFR T790M*; of these, 3 had SD ≥6 weeks (9, 12, and



*1 patient died due to progressive disease before dosing, and 1 patient was excluded due to poor prognosis

Figure 1. Study flow diagram shows patient disposition and analysis populations.

TABLE 1. Patient Baseline Characteristics

Characteristic	Adenocarcinoma (n = 50)	Nonadenocarcinoma (n = 16)[e]	Total (N = 66)
Median age, years (range)	60 (37-79)	61 (50-84)	60 (37-84)
Sex, n (%)			
Male	15 (30.0)	14 (87.5)	29 (43.9)
Female	35 (70.0)	2 (12.5)	37 (56.1)
Race, n (%)			
Caucasian	35 (70.0)	11 (68.8)	46 (69.7)
Asian	12 (24.0)	2 (12.5)	14 (21.2)
Other	3 (6.0)	3 (18.8)	6 (9.1)
Smoking status, n (%)			
Never-smoker	27 (54.0)	3 (18.8)	30 (45.5)
Current smoker	1 (2.0)	2 (12.5)	3 (4.5)
Exsmoker	22 (44.0)	11 (68.8)	33 (50.0)
ECOG performance status, n (%)			
0	18 (36.0)	5 (31.3)	23 (34.8)
1	27 (54.0)	8 (50.0)	35 (53.0)
2	5 (10.0)	3 (18.8)	8 (12.1)
Prior treatment regimens, n (%)			
1 regimen[a]	4 (8.0)	1 (6.3)	5 (7.6)
2 regimens	18 (36.0)	8 (50.0)	26 (39.4)
3 regimens	19 (38.0)	7 (43.8)	26 (39.4)
>3 regimens[b]	9 (18.0)	0	9 (13.6)
Mutational status, n (%)			
KRAS WT or EGFR sensitizing mutation	50 (100.0)	16 (100.0)	66 (100.0)
KRAS WT	39 (78.0)	15 (93.8)	54 (81.8)
KRAS unknown	11 (22.0)	1 (6.3)	12 (18.2)
EGFR WT	10 (20.0)	13 (81.3)	23 (34.8)
EGFR sensitizing mutation	24 (48.0)	2 (12.5)	26 (39.4)
Exon 19 or 21	18 (75.0)	1 (50.0)	19 (73.1)
Other	6 (25.0)	1 (50.0)	7 (26.9)
EGFR unknown	16 (32.0)	1 (6.3)	17 (25.8)
EGFR T790M secondary resistance mutation	6 (12.0)[c]	0	6 (9.1)[c]
T790M unknown	39 (78.0)	15 (93.8)	54 (81.8)
HER2 mutation	0	0	0
HER2 WT	29 (58.0)	13 (81.3)	42 (63.6)
HER2 mutation unknown	21 (42.0)	3 (18.8)	24 (36.4)
HER2 amplification positive	2 (4.0)	1 (6.3)	3 (4.5)
HER2 amplification negative	22 (44.0)	11 (68.8)	33 (50.0)
HER2 amplification unknown	26 (52.0)	4 (25.0)	30 (45.5)
Prior EGFR-directed treatment, n (%)			
Erlotinib	50 (100.0)	16 (100.0)	66 (100.0)
Gefitinib	3 (6.0)	1 (6.3)	4 (6.1)
Neratinib[d]	1 (2.0)	0	1 (1.5)
Cetuximab[d]	2 (4.0)	1 (6.3)	3 (4.5)
Response to immediately prior EGFR-directed treatment, n (%)			
CR	1 (2.0)	0	1 (1.5)
PR	13 (26.0)	0	13 (19.7)
SD	21 (42.0)	5 (31.3)	26 (39.4)
PD	9 (18.0)	10 (62.5)	19 (28.8)
Unknown	6 (12.0)	1 (6.25)	7 (10.6)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Four patients in Arm A and 1 patient in Arm B had prior systemic treatment and prior erlotinib entered as 1 regimen.

[b] Patients with >3 prior regimens includes patients with neoadjuvant and/or adjuvant therapies and/or investigational treatment regimen(s).

[c] *T790M* status was derived from archival biopsies for 4 patients and fresh baseline biopsies for 2 patients. Three of the 4 patients with *T790M* status ascertained from an archival biopsy initiated dacomitinib more than 90 days after discontinuing from erlotinib.

[d] Patients previously treated with investigational EGFR-directed therapies were eligible to participate in the study and did not represent protocol deviations, provided the study sponsor provided written agreement.

[e] Squamous, n = 12.

12 weeks, respectively) and 3 had progressive disease (PD).

Of the 36 patients with SD as BOR (median duration, 15 weeks), 10 patients (28%) had prolonged clinical benefit (SD, ≥6 months); of these, 5 patients had *EGFR*-mutant tumors, 3 had *EGFR* wild-type tumors, and 2 had tumors of unknown *EGFR* status. Of 56 patients with both baseline and ≥1 postbaseline

TABLE 2. Summary of Best Overall Response Per RECIST by Investigator Assessment, PFS, and OS

	Adenocarcinoma Arm A	Nonadenocarcinoma Arm B	Total
Overall Patient Population			
No. of patients evaluable, n	42	16	58
Objective response (CR + PR), n (%) [95% exact CI][a]	2 (5) [1-16]	1 (6) [0-30]	3 (5) [1-14]
P value[b]	0.372	0.149	–
Clinical benefit (CR + PR + SD ≥ 24 weeks), n (%) [95% exact CI][a]	10 (24) [12-40]	3 (19) [4-46]	13 (22.4) [13-35]
Duration of response, weeks	24[c], 66[d]	12[e]	NA
No. of patients enrolled, n	50	16	66
No. of PFS events[f], n (%)	40 (80)	14 (88)	54 (82)
PFS, weeks [95% CI]	12 [8-20]	11 [6-18]	12 [9-19]
PFS_{6M}, % [95% CI]	24 [12-38]	8 [1-30]	20 [11-32]
No. of deaths, n (%)	33 (66)	14 (88)	47 (71)
OS, weeks [95% CI]	45 [29-73]	27 [10-36]	37 [28-57]
OS_{6M}, % [95% CI]	72 [57-82]	50 [25-71]	66 [53-76]
OS_{12M},% [95% CI]	46 [31-60]	22 [6-45]	40 [28-52]
Patients With *EGFR*-Mutant Tumors			
No. of patients evaluable, n	23	2	25
Objective response (CR + PR), n (%) [95% exact CI][a]	2[g] (9) [1-28]	0	2[g] (8) [1-26]
Clinical benefit (CR + PR + SD ≥24 weeks), n (%) [95% exact CI][a]	7 (30) [13-53]	0	7 (28) [12-49]
No. of patients, n	24	2	26
No. of PFS events[f], n (%)	19 (79)	2 (100)	21 (81)
PFS, weeks [95% CI]	18 [6-30]	21 [17-24]	18 [9-29]
PFS_{6M}, % [95% CI]	36 [16-57]	–	32 [14-52]
No. of deaths, n (%)	17 (71)	1 (50)	18 (69)
OS, weeks [95% CI]	59 [42-76]	– [24, –]	57 [42-75]
OS_{6M}, % [95% CI]	83 [62-93]	50 [1-91]	81 [60-92]
OS_{12M}, % [95% CI]	61 [38-77]	–	59 [37-76]
Patients With *EGFR* Wild-Type Tumors			
No. of patients evaluable, n	7	13	20
Objective response (CR + PR), n (%) [95% exact CI][a]	0 [0-41]	1[h] (8) [0-36]	1[h] (5) [0-25]
Clinical benefit (CR + PR + SD ≥24 weeks), n (%) [95% exact CI][a]	2 (29) [4-71]	2 (15) [2-45]	4 (20) [6-44]
No. of patients, n	10	13	23
No. of PFS events[f], n (%)	8 (80)	11 (85)	19 (83)
PFS, weeks [95% CI]	8 [2-25]	9 [5-18]	8 [5-18]
PFS probability at 6 months [95% CI]	14 [1-45]	–	6 [0-25]
No. of deaths, n (%)	6 (60)	12 (92)	18 (78)
OS, weeks	36 [2, –]	26 [8-36]	26 [10-47]
Survival probability at 6 months [95% CI]	50 [18-75]	46 [19-70]	48 [27-66]
Survival probability at 12 months [95% CI]	40 [12-67]	23 [6-48]	30 [14-49]

A total of 12 patients were censored for PFS, 10 in arm A and 2 in arm B (Arm A: 7 patients discontinued treatment before the first on-study assessment [4 because of AE and 3 because of global deterioration]; 1 had inadequate baseline assessment; 1 was still ongoing with study treatment; 1 was no longer willing to participate and had no PD documented. Arm B: 1 patient discontinued because of AE and had SD; 1 was no longer willing to participate and had no PD documented).

[a] Using exact method based on binomial distribution.

[b] For arm A: one-sided *P*-value for the hypothesis testing H_0: ORR was ≤5% using exact binomial test. For arm B: one-sided *P*-value for the hypothesis testing H_0: ORR was ≤1% using exact binomial test.

[c] Confirmed *EGFR* mutation.

[d] *EGFR* status unknown.

[e] Confirmed *EGFR* wild type.

[f] Objective progression or death.

[g] One patient had *E746_A750del5*, exon 19; 1 patient had *G719C*, exon 18 and *S768I*, exon 20.

[h] This patient had *HER2* amplification and mutation.

Abbreviations: CI, confidence interval; CR, complete response; H_0, null hypothesis; NA, not applicable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

tumor measurement, 26 (46%) had some degree of tumor shrinkage (Fig. 2). Among patients with tumor shrinkage, 6 (23%) and 12 (46%) were confirmed as having *EGFR*-WT tumors and *EGFR*-mutant tumors, respectively; 8 (31%) had tumors of unknown *EGFR* status. Tumor shrinkage was noted in 1 patient with an *EGFR T790M* tumor; all other *EGFR T790M* tumors increased in size.

Progression-Free Survival

Overall median PFS (n = 66) was 12 weeks with 54 (82%) patients reaching PFS events, and similar values in the adenocarcinoma and nonadenocarcinoma populations. Median PFS in the adenocarcinoma group was 12 weeks based on 50 patients. In the nonadenocarcinoma group, median PFS was 11 weeks (Fig. 3A). Median PFS in patients with *EGFR* mutation-positive tumors was 18

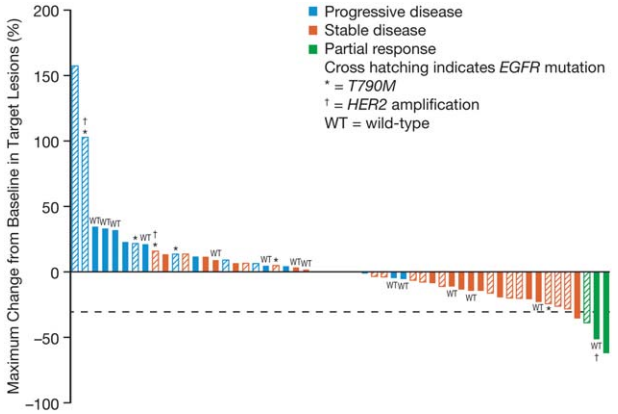


Figure 2. Maximum percentage change is shown in target lesions per RECIST (Response Evaluation Criteria in Solid Tumors) in 56 patients with both a baseline and at least one on-study measurement reflected in the database. Six patients had no change in the size of their tumor; of these, 1 had *EGFR* mutation, 1 had *EGFR* of unknown status, and 4 had *EGFR* wild-type tumors.

weeks based on 26 patients, with 21 (81%) achieving PFS events; this median was longer than that seen in the overall population. The 6 patients with documented *T790M* had a median PFS of 7 weeks, which was similar to that of patients with *EGFR* wild-type tumors (8 weeks).

Overall Survival

At the time of data cutoff, 47 patients (71%) had died and median OS was 37 weeks in the overall population, 45 weeks in patients with adenocarcinoma, and 27 weeks in patients with nonadenocarcinoma (Fig. 3B). Of the 26 patients with *EGFR* mutation-positive tumors (both arms), median OS was 57 weeks, OS_{6M} was 81%, and OS_{12M} was 59%.

Safety and Tolerability

The majority of treatment-related AEs were of grade 1 or 2 severity (Table 3) and were manageable with standard supportive care. Common events included diarrhea (85%), dermatitis acneiform (68%), dry skin (38%), fatigue (38%), exfoliative rash (24%), stomatitis (24%), decreased appetite (23%), and pruritus (23%). One patient experienced treatment-related grade 4 AEs of dyspnea and pulmonary embolism considered by the investigator to be possibly related to study drug; 18 patients (27%) experienced treatment-related AEs with a maximum severity of grade 3. The majority of patients (n = 44, 67%) did not require a dose reduction, and interruption of daily dosing was seen in 33% for evaluation and management of AEs. Of the 22 patients who did

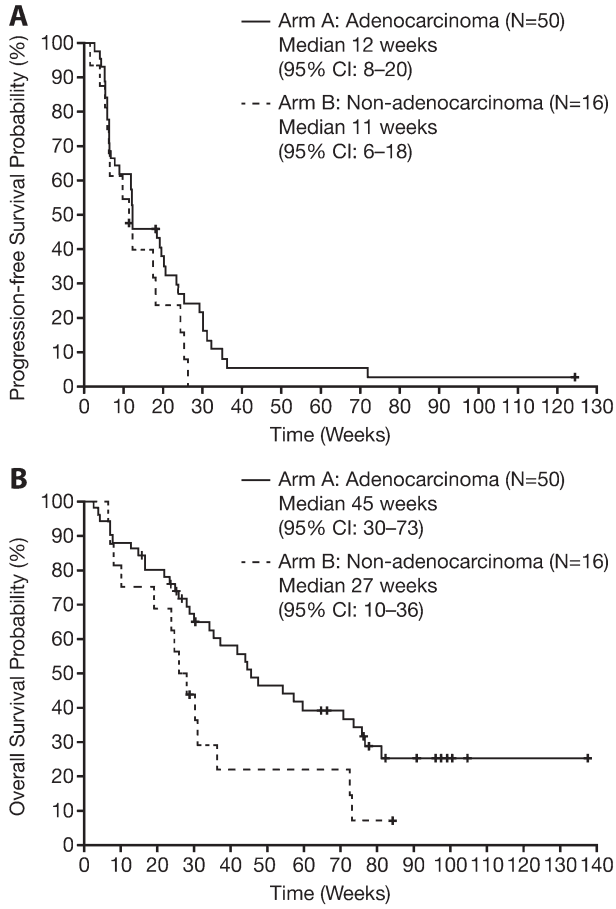


Figure 3. Kaplan-Meier curves show (A) progression-free survival and (B) overall survival by arm (all patients). CI indicates confidence interval.

require dose reduction, 17 patients had 1 dose reduction and 5 had 2 dose reductions. AEs resulting in dose modification were predominantly dermatologic or gastrointestinal. Six patients permanently discontinued dacomitinib due to treatment-related AEs, which included grade 4 dyspnea (day 8) and grade 4 pulmonary embolism (day 9) (both in a single patient); grade 3 fatigue (day 14); grade 3 exfoliative rash (day 134); grade 2 allergic dermatitis (day 3); grade 2 fatigue (day 85); and grade 1 fatigue (day 43). Twelve deaths occurred within 28 days following the last dose of dacomitinib and were reported as serious AEs; none was considered to be treatment-related.

Patient-Reported Outcomes

Completion rates for the EORTC QLQ-C30/-LC13 and DLQI questionnaires were high throughout the study (generally >90% of patients answered at least one question).

Patients with radiographic disease control reported improvement in lung cancer symptoms of dyspnea,

TABLE 3. Treatment-Related Adverse Events Occurring in ≥10% of Patients in the Overall Population (N = 66) and Hematologic Laboratory Values by Maximum CTCAE Grade (All Cycles; N = 66)

Adverse Event	Grade 1/2 n (%)	Grade 3 n (%)	Total n (%)
Any adverse events	46 (69.7)	18 (27.3)[a]	65 (98.5)
Diarrhea	48 (72.7)	8 (12.1)	56 (84.8)
Dermatitis acneiform	41 (62.1)	4 (6.1)	45 (68.2)
Dry skin	25 (37.9)	0	25 (37.9)
Fatigue	23 (34.8)	2 (3.0)	25 (37.9)
Exfoliative rash	14 (21.2)	2 (3.0)	16 (24.2)
Stomatitis	15 (22.7)	1 (1.5)	16 (24.2)
Decreased appetite	15 (22.7)	0	15 (22.7)
Pruritus	12 (18.2)	3 (4.5)	15 (22.7)
Nausea	13 (19.7)	0	13 (19.7)
Vomiting	8 (12.1)	1 (1.5)	9 (13.6)
Aspartate aminotransferase increased	8 (12.1)	0	8 (12.1)
Mucosal inflammation	7 (10.6)	0	7 (10.6)

Hematologic Laboratory Values	Grade 1/2 n (%)	Grade 3 n (%)	Total n (%)
Hemoglobin	36 (54.5)	1 (1.5)	50 (75.8)
Lymphopenia	10 (15.2)	12 (18.2)[b]	40 (60.6)
Neutropenia	2 (3.0)	1 (1.5)	4 (6.1)
Thrombocytopenia	4 (6.1)	1 (1.5)[c]	5 (7.6)
Leukopenia	10 (15.2)	0	11 (16.7)

[a] Includes two grade 4 events (dyspnea and pulmonary embolism), both experienced by the same patient.
[b] Includes 2 patients with grade 4 events.
[c] Grade 4.

cough, pain in chest, and pain in arm/shoulder relative to baseline scores, first observed after 3 weeks on therapy (Supporting Fig. 1A). Diarrhea was the most commonly reported class-related AE; diarrhea peaked at cycle 3, day 1 (week 6) and remained stable over time (Supporting Fig. 1B). With a score of 0 = no symptoms and 100 = most symptoms, patients on dacomitinib reported scores that were at the midpoint in the range at their worst. The impact of dacomitinib on PRO for NSCLC symptoms and dermatologic toxicity has been previously presented, and will be subsequently reported in full (Campbell AK et al; unpublished data).

Pharmacokinetics

PK parameters (overall and by histology) following a single dose (cycle 1 day 1), and mean C_{trough} values after multiple doses for dose-compliant patients (Supporting Table 3) were consistent with those previously reported.[5,15]

Pharmacodynamics

Soluble HER2 and EGFR levels were slightly decreased on day 1 of most cycles compared with baseline for most patients. One patient with nonadenocarcinoma demonstrating *HER2* amplification had elevated baseline soluble HER2 that significantly declined to population normal baseline levels upon treatment with dacomitinib. This patient's tumor also demonstrated a PR.[16,17]

DISCUSSION

In this phase 2 trial, dacomitinib demonstrated an overall response rate of 5% but the primary endpoint of this study was not met. Three PRs were observed, 2 in patients with *EGFR* mutation-positive tumors and 1 in a patient whose tumor was *EGFR* wild-type with *HER2* amplification.[16,17] In contrast, patients with known *EGFR T790M* did not respond to dacomitinib therapy despite efficacy in preclinical models. These observations could be due to the presence of concurrent drug resistance mechanisms (such as *MET* amplification),[18] or to the inability of dacomitinib to fully inhibit EGFR in tumors harboring *EGFR T790M* at the doses currently under clinical investigation.[5] Strategies to improve EGFR inhibition in *EGFR T790M* cancers include the combination of irreversible EGFR inhibitors with the EGFR-directed antibody cetuximab (as reported for afatinib plus cetuximab)[19]; the development of more potent and specific inhibitors of EGFR *T790M*[20,21]; and the use of intermittent but high doses of existing irreversible EGFR inhibitors.[18] In contrast, where resistance is

mediated by compensatory signaling pathways, or tumors harbor more than one concomitant drug resistance mechanism, combination strategies with targeted agents in appropriately selected patients will be necessary to treat such cancers (eg, inhibition of the MET pathway).

In the absence of a known oncogene addiction, patients with wild-type EGFR may still benefit from EGFR-directed therapy in the absence of a RECIST-defined radiographic response; endpoints such as PFS, and patient report of HRQoL and symptom relief have become increasingly important in a noncurative setting.[22] This is demonstrated in the BR21 trial of erlotinib versus placebo, where the ORR was low and yet was associated with improvements versus placebo in OS and NSCLC symptoms.[10,23] In the current study in refractory NSCLC, 10 of 36 patients with SD as BOR derived prolonged clinical benefit (SD $\geq$ 6 months) with dacomitinib; patients also reported a rapid onset of improvement in key lung cancer symptoms, with symptomatic improvements remaining durable over the course of therapy. Common AEs were typically gastrointestinal or dermatologic and consistent with targeting EGFR.[24,25] By patient report, both gastrointestinal and dermatologic symptoms peaked early in treatment and stabilized or improved over time (Campbell AK et al; unpublished data).

The benefits seen in this study may reflect dacomitinib's broader mode of action in targeting all kinase-active HER family members, irreversible binding to the tyrosine kinase domain, retreatment in some of those patients with an EGFR-driven tumor following a period off treatment after a prior selective EGFR TKI, or other as yet to be determined factors. Data from this and other phase 1 and 2 studies in post-EGFR TKI settings,[5,7] and from a head-to-head trial comparing dacomitinib with erlotinib in the second-line setting,[8] suggest that dacomitinib has clinically relevant activity in patients with NSCLC who do not harbor *KRAS* mutations. However, in the absence of a control arm, it remains unclear if this degree of benefit seen here could be due to patient selection or favorable prognostic factors. A phase 3 trial is underway to determine the efficacy and safety of dacomitinib compared with erlotinib in patients with *KRAS* wild-type NSCLC for whom first-line chemotherapy has failed (ARCHER 1009; ClinicalTrials.gov identifier NCT01360554).

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CONFLICT OF INTEREST DISCLOSURE

Drs. Ruiz-Garcia, Liang, Taylor, Gernhardt, and O'Connell are employees of Pfizer and own Pfizer stock. Stephen Letrent and an immediate family member are employees of Pfizer and own Pfizer stock. Dr. Reckamp received research funding from Pfizer. Dr. Camidge served Pfizer in an advisory role. Dr. Engelman received honoraria from Genentech/Roche, and received research funding from Novartis. He also received remuneration from Pfizer for use of cell lines for which he is a coinventor, and has an EGFR/MET patent that has been licensed by Ventana and owned by Roche (no compensation to date). Dr. Koczywas received honoraria from Pfizer and Genentech. Dr. Gadgeel received honoraria from Pfizer. Alicyn K. Campbell and an immediate family member were previously employed by Pfizer (neither hold current employment with Pfizer). Dr. Campbell is currently employed by Genentech, a member of the Roche Group. Dr. Jänne has been a consultant for Boehringer-Ingelheim, Genentech/Roche, AstraZeneca, and Pfizer. Drs. Giaccone, Khuri, and Rajan have no conflicts of interest to disclose.

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