Safety and Efficacy of Dacomitinib in Korean Patients with *KRAS* Wild-Type Advanced Non–Small-Cell Lung Cancer Refractory to Chemotherapy and Erlotinib or Gefitinib

A Phase I/II Trial

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Introduction: Dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor ([HER]-1/EGFR, HER-2, and HER-4) tyrosine kinase inhibitor, demonstrated antitumor activity in Western patients with non–small-cell lung cancer (NSCLC) at a dose of 45 mg once daily. We report data from a phase I/II, multicenter, open-label study of Korean patients with refractory *KRAS* wild-type adenocarcinoma NSCLC (defined as patients with evidence of disease progression during or within 6 months of treatment with chemotherapy and gefitinib or erlotinib).

Methods: The phase I dose-finding portion identified the recommended phase II dose (RP2D) in Korean patients, evaluated safety, and characterized the pharmacokinetics of dacomitinib. In the phase II portion, patients received dacomitinib at the RP2D. The primary end point was progression-free survival at 4 months (PFS_{4m}).

Results: Twelve patients enrolled in phase I, and 43 patients enrolled in phase II at the RP2D of 45 mg once daily. In phase II, PFS_{4m} was 47.2% (95% confidence interval [CI], 31.6–61.3; one-sided *p*-value = 0.0007). Median PFS was 15.4 weeks (95% CI, 9.7–17.6); median overall survival was 46.3 weeks (95% CI, 32.7–not reached); and the objective response rate was 17.1% (95% CI, 7.2–32.1). Common treatment-related adverse events were dermatitis acneiform, diarrhea, and paronychia; there were no treatment-related grade 4 or 5 adverse events. Pharmacokinetic parameters of dacomitinib in Korean patients were similar to those reported in Western patients. By patient report, NSCLC symptoms "cough" and "pain" showed improvement within 3 weeks of initiating treatment.

Conclusions: Dacomitinib was well tolerated and had antitumor activity in Korean patients with NSCLC who had previously progressed on chemotherapy and an epidermal growth factor receptor tyrosine kinase inhibitor.

Key Words: Dacomitinib, Non–small-cell lung cancer, Erlotinib, Gefitinib, Refractory.

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Patients with non–small-cell lung cancer (NSCLC) have limited treatment options after failure of reversible epidermal growth factor receptor (HER1/EGFR) inhibitors, erlotinib or gefitinib, and chemotherapy. Dacomitinib (PF-00299804) is an orally bioavailable, irreversible, small-molecule inhibitor of HER1/EGFR, human epidermal growth factor receptor 2 (HER2), and HER4 tyrosine kinases.[1] Dacomitinib has preclinical activity in NSCLC models with *EGFR*-activating mutations, and with the *EGFR* "gatekeeper" resistance *T790M* mutation, present in 50% of patients with *EGFR* mutations

who develop gefitinib or erlotinib resistance.[1–5] Clinical trials in Western patients have identified a recommended phase II dose (RP2D) of dacomitinib of 45 mg once daily (QD), with associated antitumor activity in NSCLC.[6]

KRAS is a downstream effector of *EGFR* signal transduction; tumors with activated *KRAS* might therefore be expected to be resistant to *EGFR* inhibition.[7,8] Indeed, *KRAS* mutation is a negative predictor of response to EGFR tyrosine kinase inhibitors (TKIs).[9] In addition, primary oncogenic mutations in NSCLC are usually mutually exclusive.[10] *EGFR* mutations have been reported in approximately 50% of Asian patients,[11] and *KRAS* mutations have been reported in 5% to 10% of Asian patients with adenocarcinoma.[12] A selection strategy that includes only patients with *KRAS* wild-type tumors would enrich for a population with over a 50% chance of harboring an *EGFR* mutation and be more likely to respond to targeted therapy.

We report the results of a Korean multicenter, open-label, single-arm, phase I/II trial of single-agent dacomitinib in Asian patients with *KRAS* wild-type advanced NSCLC. Patients had received erlotinib or gefitinib and more than or equal to one regimen of chemotherapy, with progressive disease (PD) during or less than or equal to 6 months after treatment (NCT00553254). The aim was to establish the RP2D of dacomitinib in this setting and to assess whether clinical activity in refractory NSCLC warrants further development in this population.

PATIENTS AND METHODS

Patient Population

Eligible patients were more than or equal to 18 years with histologically or cytologically confirmed metastatic (stage 3B/4) adenocarcinoma NSCLC, which was *KRAS* wild type. Patients had received more than or equal to one regimen of chemotherapy (including ≥1 platinum-based therapy) and erlotinib or gefitinib with evidence of PD less than or equal to 6 months after treatment. Patients had Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1 (phase I cohort) and 0–2 (phase II cohort); those with known active brain metastases were excluded. Further details regarding inclusion/exclusion criteria are available (see supplementary materials, Supplemental Digital Content 1, http://links.lww.com/JTO/A629).

Trial Design and Treatment

In the setting described above, the phase I primary objective was to define the RP2D of dacomitinib and evaluate safety and tolerability. The phase II primary objective was to assess the antitumor efficacy of single-agent dacomitinib administered QD, using progression-free survival (PFS) at 4 months (PFS_{4m}). As evolving published data[13] suggested that PFS and overall survival (OS) can be improved with EGFR TKI treatment despite a low objective response rate (ORR),[14] the original phase II primary end point, ORR, was amended to PFS_{4m} as this was considered a more clinically meaningful efficacy end point.

Phase I secondary objectives included characterization of single- and multiple-dose pharmacokinetics (PK) of dacomitinib; analysis of pre- and post-treatment serum levels of HER2 and EGFR extracellular domains, and exploration of relationships between changes in these serum proteins and clinical response to dacomitinib; and description of preliminary antitumor activity using Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v 1.0).[15] Phase II secondary objectives included confirmation of the safety and tolerability of dacomitinib; assessment of antitumor activity using ORR, duration of overall response, PFS at 6 months, and OS at 6 months; characterization of multiple-dose PK of dacomitinib; analysis of pre- and post-treatment serum levels of the soluble HER2 and EGFR extracellular domains; and exploration of patient-reported outcomes (PROs) of health-related quality of life and disease/treatment-related symptoms.

In phase I, successive cohorts of six patients received escalating doses of oral dacomitinib, starting at 30 mg QD. If less than two of six patients (i.e., <33%) experienced a dose-limiting toxicity (DLT) at 30 mg QD, the next six patients received 45 mg QD. A DLT comprised any of the following during the first 21 days of cycle 1 (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0): any treatment-related grade greater than or equal to 3 nonhematologic toxicity (including grade 3 or 4 nausea, vomiting, or diarrhea despite adequate/maximal medical intervention and/or prophylaxis); treatment-related toxicity that delayed dacomitinib dosing by more than 14 days; treatment-related grade 4 neutropenia for more than or equal to 5 days or febrile neutropenia; or treatment-related grade 4 thrombocytopenia or bleeding requiring platelet transfusion. The maximum tolerated dose was the highest dose resulting in first-cycle DLTs in less than two of six patients, assessed up to a maximum dose of 45 mg.

During phase I, a single lead-in dose of dacomitinib was administered between completion of screening and day −9. Assigned treatment was then initiated on day 1. In phase II, patients received the RP2D of dacomitinib determined in phase I; dosing started on day 1 of each cycle without a lead-in period. Dacomitinib was administered at approximately the same time each day (with water, on an empty stomach) in 21-day cycles (defined for the purposes of scheduling treatment visits). Patients continued dacomitinib until unacceptable toxicity, disease progression, withdrawal from the trial, or death. Dose reductions or delays were permitted throughout the trial for treatment-related grade 3 or 4 toxicity or for intolerable grade 2 toxicity despite optimal supportive care. Treatment delay or interruption for more than 2 consecutive weeks due to dacomitinib-related toxicity resulted in the patient being withdrawn from the trial. All patients were followed for survival for at least 12 months; patients who discontinued treatment for reasons other than PD were followed until disease progression or the start of new cancer treatment, whichever occurred first.

This trial was approved by an Institutional Review Board/Independent Ethics Committee at each participating center. All patients provided written, signed informed consent before entry into the trial.

Evaluation of Safety and Tolerability

The RP2D was determined through evaluation of DLTs, as described above. Safety and tolerability were assessed using standard methodology up to the 28-day period after final administration of dacomitinib or until all drug-related

toxicities had resolved or were deemed irreversible, whichever was later. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. For all patients receiving a lead-in dose in phase I, electrocardiograms and vital signs were assessed at screening and 6, 24, and 144 hours postdose; physical and skin exams, hematology, coagulation panel, blood chemistry, and urinalysis were also performed at screening and 24 hours and 144 hours (6 days) postdose.

Evaluation of Antitumor Activity

PFS_{4m} was defined as the proportion of patients who were alive without disease progression at 4 months relative to all patients enrolled. Evaluation of antitumor activity was based on objective tumor assessments (RECIST version 1.0),[15] per investigator assessment, performed within 4 weeks before the start of treatment and every 6 weeks on study or when PD was suspected.

Evaluation of Patient-Reported Outcomes

PROs were measured using the 30-question European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), its 13-question lung cancer module (LC13),[16–18] and the 10-question Dermatology Life Quality Index.[19] All questionnaires were validated in Korean and completed before any clinical assessments at screening (baseline), on day 1 of cycle 2 and each subsequent cycle, and at the end of treatment. Completion rates were calculated as the number of subjects completing the assessment divided by the total number of subjects eligible for the assessment.

Pharmacokinetic Analyses

Plasma samples were collected at prespecified intervals pre- and postdose throughout the trial (see supplementary materials for further details, Supplemental Digital Content 1, http://links.lww.com/JTO/A629). Plasma dacomitinib concentrations were determined at Alta Analytical Laboratory (El Dorado Hills, CA) using a validated, sensitive high-performance liquid chromatography—atomic pressure ionization tandem mass spectrometric method in compliance with Pfizer standard operating procedures.

Pharmacokinetic parameters were derived using a noncompartmental approach (eNCA version 2.2, Pfizer Inc., Groton, CT), and after a single-dose administration (D-9) included maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), terminal elimination half-life ($t_{1/2}$), area under the plasma concentration–time curve from 0 to 24 hours after a single dose (AUC_{24}), area under the plasma concentration–time curve from 0 to infinity (AUC_{inf}), and apparent oral clearance (CL/F). Parameters derived after multiple-dose administration (C1D14) included C_{max}, T_{max}, CL/F, area under the plasma concentration–time curve from 0 to 24 hours at steady state (AUC_{tau}), predose trough concentration (C_{trough}), and accumulation ratio (R_{ac}, the ratio of AUC_{tau} to AUC_{24}). Predose trough concentrations (C_{trough}) on day 1 of cycles 2 to 4 together with C_{trough} concentrations on cycle 1 day 14 are summarized by visit.

Pharmacodynamic (Biomarker) Analysis

In phases I and II, serum levels of soluble protein biomarkers (HER2 and EGFR extracellular domains) were assessed at baseline and before dosing on day 1 of cycle 1 and every two cycles thereafter. Potential correlations between biomarker levels and efficacy, response, and tumor shrinkage were investigated.

Statistical Analyses

No specific statistical hypothesis testing for safety, PK, and efficacy was planned for the phase I portion of the trial. The sample size was determined empirically; it was expected that approximately 18 patients would be enrolled. For the phase II portion of the trial, the Fleming single-stage design (amended from a Simon two-stage optimal design) was used to test the null hypothesis that PFS_{4m} was less than or equal to 25%. Enrollment of 42 patients was planned. The type I error was 10%, and the design had 80% power to reject the null hypothesis when the true PFS_{4m} rate was 40%.

Baseline characteristics and time-to-event efficacy end points were evaluated in the intent-to-treat population. Safety was evaluated in the as-treated population and response assessed in the response-evaluable population.

RESULTS

Patient Characteristics and Disposition

Between February 2008 and July 2008, 12 patients were enrolled in phase I; 43 patients were subsequently enrolled in phase II (September 2008–March 2010). Most patients were heavily pretreated (58.3% of patients in phase I had received two regimens, and 60.5% of patients in phase II had received >3 prior regimens). All patients had received prior erlotinib or gefitinib, and three patients had received more than one prior TKI (Table 1); for the overall population ($N = 55$, phases I and II), the most recent prior EGFR inhibitor was erlotinib, 26 patients, and gefitinib, 29 patients; 61.5% of patients who received prior erlotinib and 20.7% who received prior gefitinib started study drug within 3 months of discontinuing the prior EGFR TKI. Overall, the median duration of the most recent prior erlotinib/gefitinib regimen was 4.6 months (range, 0.9–37.2 months) for erlotinib and 6.9 months (range, 0.9–40.4 months) for gefitinib. There were eight partial responses (PRs) to prior erlotinib and 12 PRs to prior gefitinib. Most patients (83.3% of phase I and 65.1% of phase II) were never smokers. Molecular screening of tumor tissue was required to confirm *KRAS* wild type. *EGFR* and *HER2* mutation status was not required. Among 14 patients with *EGFR*-mutant NSCLC, *EGFR* mutation location was unspecified in four (28.6%) patients, three (21.4%) had exon 19 deletion, three (21.4%) had exon 21 mutation, two (14.3%) had exon 20 insertion mutation (a known EGFR inhibitor resistance mutation), one (7.1%) had exon 20/21 + *T790M* (a known EGFR inhibitor resistance mutation), and one (7.1%) had exon 18/21 dual mutation.

Maximum Tolerated Dose

No DLTs were observed up to a dose of 45 mg QD, which was confirmed as the RP2D in Korean patients

TABLE 1. Patient Baseline Characteristics by Study Phase

Characteristic	Phase I (n = 12)	Phase II (n = 43)
Median age, yr (range)	51.5 (31–78)	59.0 (40–72)
Gender, *n* (%)		
Male	3 (25.0)	20 (46.5)
Female	9 (75.0)	23 (53.5)
Smoking history, *n* (%)		
Never	10 (83.3)	28 (65.1)
Current	0	1 (2.3)
Ex-smoker[a]	2 (16.7)	14 (32.5)
Prior systemic treatment, *n* (%)		
1 regimen	0	0
2 regimens	7 (58.3)	6 (14.0)
3 regimens	1 (8.3)	11 (25.6)
>3 regimens	4 (33.3)	26 (60.5)
Prior EGFR inhibitors, *n* (%)[b]		
Erlotinib	5 (41.7)	22 (51.2)
Gefitinib	7 (58.3)	22 (51.2)
Vandetanib	0	1 (2.3)
Median duration of most recent prior EGFR inhibitor, mo (range)		
Erlotinib	4.8 (0.9–14.5)	4.6 (1.0–37.2)
Gefitinib	2.9 (0.9–10.9)	7.6 (0.9–40.4)
Prior response		
Erlotinib	1 PR, 2 SD, 2 PD	7 PR, 10 SD, 4 PD
Gefitinib	2 PR, 3 SD, 2 PD	10 PR, 8 SD, 4 PD
ECOG performance status, *n* (%)		
0	2 (16.7)	11 (25.6)
1	10 (83.3)	29 (67.4)
2	0	3 (7.0)
EGFR mutation status, *n* (%)		
Wild type	3 (25.0)	3 (7.0)
Mutant	2 (16.6)	12 (27.9)
Unknown	7 (58.3)	28 (65.1)
HER2 mutation status, *n* (%)		
Wild type	0	9 (20.9)
Mutant	0	1 (2.3)
Unknown	12 (100.0)	33 (76.7)

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

[b]For phase II, three patients received more than one EGFR TKI regimen: one patient received two nonconsecutive regimens of erlotinib; one patient received erlotinib before receiving gefitinib (these regimens were nonconsecutive); and one patient received vandetanib followed by a consecutive regimen of gefitinib.

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; *EGFR*, epidermal growth factor receptor gene; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

with *KRAS* wild-type advanced NSCLC, consistent with Western studies.

Safety and Tolerability

The incidence of all-grade treatment-related adverse events in the overall population (N = 55) was 53 (96.4%). The most common treatment-related adverse events were dermatitis acneiform (81.8%), diarrhea (78.2%), paronychia (63.6%), stomatitis (45.5%), and palmar–plantar erythrodysesthesia syndrome (32.7%) (Table 2). Most frequent treatment-related grade 3 adverse events (all occurring in the phase II cohort, i.e., 45 mg (n = 43)) were diarrhea (n = 6; 14.0%), paronychia (n = 4; 9.3%), and dermatitis acneiform (n = 2; 4.7%). Three treatment-related hematologic adverse events (all occurring in the phase II cohort) included hemoglobin (n = 1; 2.4%) and lymphocytes (n = 2; 4.8%). No patients had treatment-related grade 4 or 5 adverse events. Serious adverse events were experienced by 10 patients (phase I, one patient; phase II, nine patients); only one serious adverse event (one patient with diarrhea during phase II) was considered to be related to study treatment.

No patient discontinued for treatment-related adverse events. Most adverse events resulting in temporary discontinuation of treatment or dose reduction were treatment-related grade 2 or 3 diarrhea or skin events that subsequently resolved. There were no treatment-related deaths. The median duration of treatment was 85.0 days in phase I and 97.0 days in phase II. Three patients (25.0%) in phase I and 21 patients (48.8%) in phase II had a missed dose, and 0 and 15 patients (34.9%) required a dose reduction in phase I and II, respectively.

Efficacy

Progression-free survival

The primary efficacy objective of the study was met; the estimated PFS_{4m} in phase II was 47.2% (95% confidence interval [CI], 31.6–61.3), with a 1-sided p-value of 0.0007 for H_0: PFS_{4m} less than or equal to 25%. This was associated with a median PFS of 15.4 weeks (95% CI, 9.7–17.6) (Fig. 1*A*) and an estimated PFS rate at 6 months of 24.8% (95% CI, 12.9–38.7). Median PFS for all patients (N = 55) was 13.7 weeks (95% CI, 11.4–17.6). Fourteen patients (25.5%) had an *EGFR* mutation (two patients in phase I starting from 30 mg and 12 patients in phase II). The 12 patients in phase II whose tumors were *EGFR* mutation positive had a median PFS of 15.4 weeks (95% CI, 5.4–35.6).

Overall survival

In phase II, OS was analyzed when 25 patients (58.1%) had died; median OS was 46.3 weeks (95% CI, 32.7–not reached) (Fig. 1*B*). The probability of survival at 6 and 12 months was 80.7% (95% CI, 65.1–89.9) and 39.1% (95% CI, 24.0–53.9), respectively.

OS was analyzed in the overall population (N = 55) when 34 patients (61.8%) had died; median OS was 47.1 weeks (95% CI, 32.7–60.6).

Best overall response

There were 41 response-evaluable patients in phase II (two patients without an on-study tumor assessment were excluded from the analysis; one with *EGFR* mutation in exon 21 and one with unknown *EGFR* status), of whom seven (17.1%) achieved a PR, including two with *EGFR* mutation and five with unknown *EGFR* status (see Supplementary Table 1 for additional details, Supplemental Digital Content 1, http://links.lww.com/JTO/A629); 21 (51.2%) had stable disease (SD), including two patients with an unconfirmed PR (per RECIST 1.0 definition of confirmation). The clinical benefit rate (complete response, PR or SD ≥24 weeks) in phase

TABLE 2. Treatment-Related Adverse Events (Occurring in ≥10% of Patients in Overall Population; *n* = 55) and Hematology Laboratory Values by Maximum CTCAE Grade (All Cycles)

	Phase I (*N* = 12)				Phase II (*N* = 43)				
	Grade 1	Grade 2	Grade 3	Total[a]	Grade 1	Grade 2	Grade 3	Total[a]	Total (*N* = 55)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Treatment-related adverse events									
Dermatitis acneiform	4 (33.3)	6 (50.0)	0	10 (83.3)	14 (32.6)	19 (44.2)	2 (4.7)	35 (81.4)	45 (81.8)
Diarrhea	5 (41.7)	3 (25.0)	0	8 (66.7)	19 (44.2)	10 (23.3)	6 (14.0)	35 (81.4)	43 (78.2)
Paronychia	4 (33.3)	2 (16.7)	0	6 (50.0)	13 (30.2)	12 (27.9)	4 (9.3)	29 (67.4)	35 (63.6)
Stomatitis	4 (33.3)	1 (8.3)	0	5 (41.7)	11 (25.6)	8 (18.6)	1 (2.3)	20 (46.5)	25 (45.5)
Palmar–plantar erythrodysesthesia syndrome	2 (16.7)	3 (25.0)	0	5 (41.7)	12 (27.9)	1 (2.3)	0	13 (30.2)	18 (32.7)
Dry skin	0	1 (8.3)	0	1 (8.3)	5 (11.6)	11 (25.6)	0	16 (37.2)	17 (30.9)
Pruritus	1 (8.3)	1 (8.3)	0	2 (16.7)	11 (25.6)	3 (7.0)	1 (2.3)	15 (34.9)	17 (30.9)
Decreased appetite	2 (16.7)	0	0	2 (16.7)	10 (23.3)	3 (7.0)	0	13 (30.2)	15 (27.3)
Mucosal inflammation	2 (16.7)	3 (25.0)	0	5 (41.7)	5 (11.6)	2 (4.7)	0	7 (16.3)	12 (21.8)
Fatigue	0	0	0	0	6 (14.0)	1 (2.3)	1 (2.3)	8 (18.6)	8 (14.5)
Nausea	3 (25.0)	0	0	3 (25.0)	5 (11.6)	0	0	5 (11.6)	8 (14.5)
Erythematous rash	1 (8.3)	0	0	1 (8.3)	2 (4.7)	3 (7.0)	0	5 (11.6)	6 (10.9)
	Phase I (*N* = 12)				**Phase II (*N* = 42)[b]**				
	Grade 1	**Grade 2**	**Grade 3**	**Total[c]**	**Grade 1**	**Grade 2**	**Grade 3**	**Total[b]**	**Total (*N* = 54)**
Hematology laboratory values by maximum CTCAE grade									
Hemoglobin	7 (58.3)	1 (8.3)	0	8 (66.7)	20 (47.6)	6 (14.3)	1 (2.4)	27 (64.3)	35 (64.8)
Lymphocytes	7 (58.3)	1 (8.3)	0	8 (66.7)	27 (64.3)	5 (11.9)	2 (4.8)	34 (81.0)	42 (77.8)
Neutrophils	2 (16.7)	0	0	2 (16.7)	1 (2.4)	0	0	1 (2.4)	3 (5.6)
Platelets	2 (16.7)	0	0	2 (16.7)	4 (9.5)	0	0	4 (9.5)	6 (11.1)
White blood cells	1 (8.3)	1 (8.3)	0	2 (16.7)	2 (4.8)	2 (4.8)	0	4 (9.5)	6 (11.1)

[a]No grade 4 or 5 treatment-related adverse events were reported.
[b]One patient had a missing postbaseline laboratory assessment and so was excluded.
[c]No grade 4 hematologic abnormalities.
CTCAE, Common Toxicity Criteria for Adverse Events.

II was 29.3% (95% CI, 16.1–45.5) (see Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/JTO/A629). Median duration of response for the seven patients with a PR in phase II was 60.0 weeks. A further two patients in phase I treated at 45 mg had a PR (see Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A629). Two case histories for patients with PRs are shown in Supplementary Figures 1 (Supplemental Digital Content 2, http://links.lww.com/JTO/A630) and 2 (Supplemental Digital Content 3, http://links.lww.com/JTO/A631).

Overall, 13 of 20 patients with known *EGFR* status had *EGFR* mutation and were also response-evaluable patients; of these, two patients (15.4%) had a PR (95% CI, 1.9–45.4), eight (61.5%) had SD (two patients receiving 30 mg in phase I), and three (23.1%) had PD as best overall response. In phase II, 19 of 40 patients (47.5%) with a baseline and more than or equal to one postbaseline tumor measurement had some degree of target lesion decrease from baseline (Fig. 2). Among the 19 patients with tumor shrinkage, one (5.3%) and six (31.6%) had *EGFR* wild-type and *EGFR*-mutant tumors, respectively, and 12 (63.2%) had tumors of unknown *EGFR* status. One patient with prolonged SD (249 days) as best overall response had the secondary *EGFR* resistance mutation *T790M* and experienced tumor shrinkage of 31.0% (Fig. 2). Of 20 patients with PR to prior erlotinib/gefitinib, response to dacomitinib included PR (*n* = 6), SD (*n* = 12), PD (*n* = 1), and indeterminate (*n* = 1). *EGFR* mutation status for these patients is provided in Supplementary Table 3 (Supplemental Digital Content 1, http://links.lww.com/JTO/A629). Of the 10 patients with SD of more than or equal to 24 weeks' duration in response to erlotinib or gefitinib, three had a PR, four had SD, and three had PD in response to dacomitinib.

Patient-reported outcomes

Completion rates for the EORTC-QLQ-C30/-LC13 and Dermatology Life Quality Index questionnaires were high (≥95%). Mean EORTC-QLQ-C30/-LC13 assessment

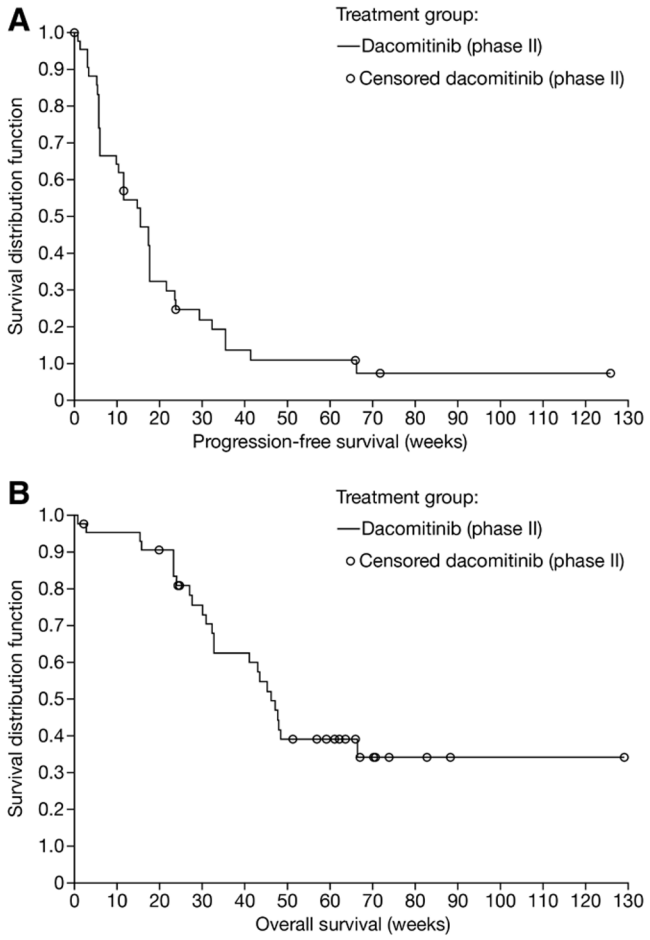


FIGURE 1. Kaplan–Meier plot of (*A*) progression-free survival and (*B*) overall survival in the phase II portion, as enrolled.

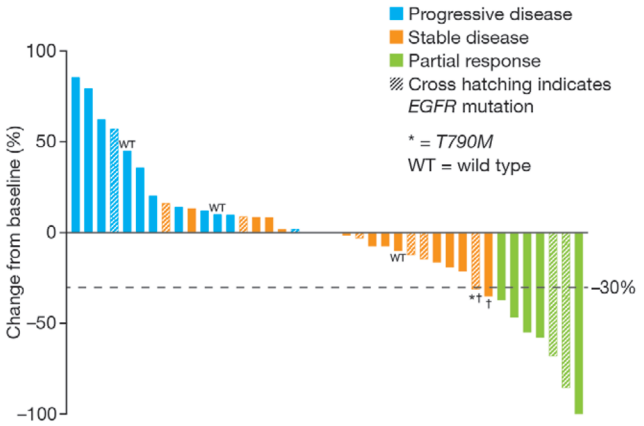


FIGURE 2. Best percent change from baseline in target lesion as assessed by RECIST in the phase II portion. *N* = 40: One patient with progressive disease in nontarget lesion but no target lesion measurement and two patients without on-study tumor scan were excluded. †Two patients had >30% reduction at one post-treatment assessment, but PR was not confirmed on a follow-up assessment and responses were classified as SD per RECIST v1.0. RECIST, Response Evaluation Criteria in Solid Tumors v1.0; PR, partial response; SD, stable disease.

scores at baseline and changes during study treatment relative to baseline are summarized and compared with previously published normative values in Supplementary Table 4 (Supplemental Digital Content 1, http://links.lww.com/JTO/A629).[20] During study treatment, patients with radiographic disease control reported improvement in lung cancer symptoms of cough, pain in chest, and pain in arm/shoulder relative to baseline scores (Fig. 3*A*). Adverse impact of diarrhea and sore mouth peaked at cycle 2, day 1 (week 3), and subsequently improved over time (Fig. 3*B*). Skin toxicity events had a longer time to onset, with a peak at cycle 5, day 1, and improved thereafter (Fig. 3*C*). Qualitatively, these results indicated that, at its worst, treatment-related skin toxicity had a "moderate effect" on patients' life over the prior week.[19] Mean baseline scores for the above six items are listed in Figure 3*D* with previously published normative values.[20]

Pharmacokinetics

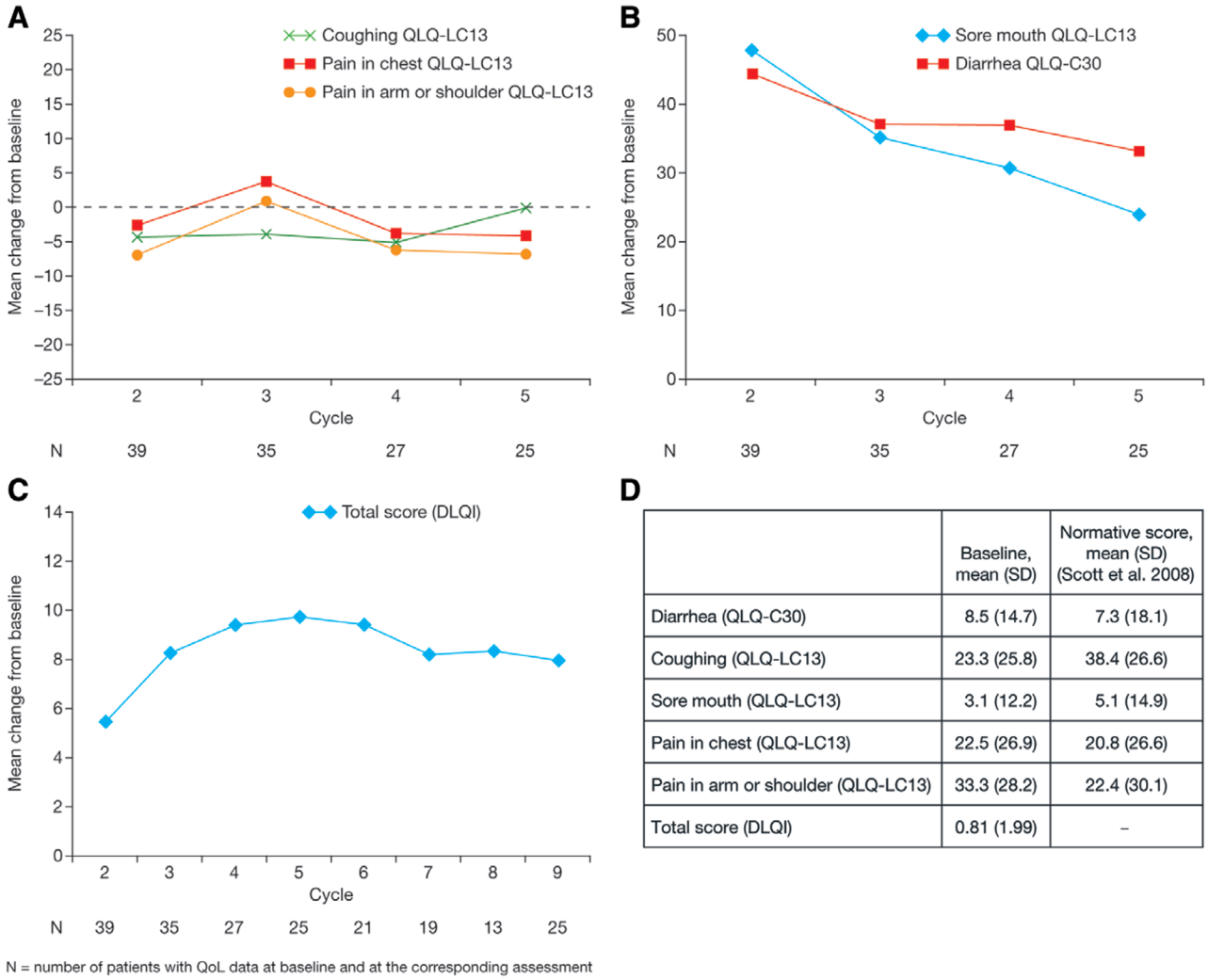
PK parameters of dacomitinib after single (day −9) and multiple doses in patients receiving consecutive doses for more than or equal to 14 days are summarized in Supplementary Table 5 (Supplemental Digital Content 1, http://links.lww.com/JTO/A629). After single-dose administration (day −9), observed median T_{max} was 8.0 hours and 5.0 hours for 30 and 45 mg doses, respectively. After multiple-dose administration (C1D14), observed median T_{max} was 5.0 and 6.1 hours for 30 mg and 45 mg dosing, respectively. Mean apparent clearance was 33.6 and 36.0 liter/hr after administration of a single oral dose of 30 and 45 mg, respectively. Mean R_{ac} was 5.3 and 5.7 for the 30 and 45 mg doses, respectively. Dose-normalized parameters such as C_{max}, AUC_{inf}, and AUC_{tau}, after a single dose or at steady state, were similar in 30 mg and 45 mg dosing cohorts (Supplementary Fig. 3, Supplemental Digital Content 4, http://links.lww.com/JTO/A632). Plasma concentration–time plots after single and multiple doses are shown in Figure 4*A* and 4*B*, respectively. As seen in previous studies, plasma exposure of dacomitinib increased with dose, with a higher exposure at 45 mg compared with 30 mg dosing after single and multiple oral dosing. Terminal elimination of dacomitinib was similar after a single oral dose of 30 or 45 mg.[6,21]

Pharmacodynamics

Mean ratios to baseline of serum levels of EGFR and HER-2 were largely unchanged in all cycles of the phase I study. Similarly, ratios to baseline of these biomarkers were not significantly changed at all cycles during phase II. No correlations were observed between changes in levels of these serum proteins and clinical response to dacomitinib (data not shown).

DISCUSSION

Dacomitinib was well tolerated in this Korean patient population; no DLTs were observed up to a dose of 45 mg QD, which was therefore confirmed as the RP2D. The RP2D and the observed safety profile were consistent with reports from Western studies[6,22,23] and a study of unselected Japanese patients, the majority of whom had NSCLC.[21] No discontinuations due to treatment-related adverse events, and no grade 4



	Baseline, mean (SD)	Normative score, mean (SD) (Scott et al. 2008)
Diarrhea (QLQ-C30)	8.5 (14.7)	7.3 (18.1)
Coughing (QLQ-LC13)	23.3 (25.8)	38.4 (26.6)
Sore mouth (QLQ-LC13)	3.1 (12.2)	5.1 (14.9)
Pain in chest (QLQ-LC13)	22.5 (26.9)	20.8 (26.6)
Pain in arm or shoulder (QLQ-LC13)	33.3 (28.2)	22.4 (30.1)
Total score (DLQI)	0.81 (1.99)	–

FIGURE 3. Mean change from baseline in (*A*) lung cancer symptoms of cough, pain in chest, and pain in arm or shoulder (EORTC QLQ-C13); (*B*) class-related adverse events of diarrhea (EORTC QLQ-C30) and sore mouth (EORTC QLQ-LC13); (*C*) skin toxicity by total scores on DLQI (Dermatology Life Quality Index). Baseline scores and equivalent normative values for the respective symptoms are listed in panel (*D*). 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. EORTC scales are scored from 0 to 100; DLQI total scores range from 0 to 30. SD, standard deviation.

or 5 adverse events, were reported in Korean patients. Adverse events (primarily skin and gastrointestinal toxicities) were consistent with the expected toxicities of EGFR TKIs,[24–26] although the incidence of paronychia (63.6%) reported here was somewhat higher than has been noted in other studies of irreversible pan-HER TKIs in the refractory, second/third-line, and first-line settings.[22,23,27,28] However, given the relatively small sample size of the current study, it is not possible to draw any wider conclusions from this observation.

Encouraging antitumor activity was observed with dacomitinib in heavily pretreated Korean patients with refractory NSCLC. The median PFS of 15.4 weeks compares favorably with a phase II study in Western patients, where the PFS for *KRAS* wild-type adenocarcinoma was 12 weeks.[29] In another single-arm phase II study, LUX-Lung 4, the irreversible EGFR/HER1 and HER2 inhibitor afatinib (BIBW 2992) demonstrated a PFS of 4.4 months and ORR of 8.2%[30]; differences from the present study included eligibility criteria of at least 12 weeks of prior TKI (thus enriching for an *EGFR*-mutant population) and conduct only in Japan. The LUX-Lung 1 phase IIb/III study evaluated afatinib in patients with NSCLC (PS 0–2) and disease progression after one or two lines of chemotherapy and erlotinib or gefitinib.[27] This study revealed improvement in median PFS of 3.3 months (95% CI, 2.79–4.40) for afatinib plus best supportive care and a hazard ratio of 0.38 ($p < 0.0001$ relative to placebo). However, there was no improvement in median OS (afatinib: 10.8 months [95% CI, 10.0–12.0], placebo: 12.0 months [95% CI, 10.2–14.3]; hazard ratio, 1.08; 95% CI, 0.86–1.35; $p = 0.74$). These results suggest that irreversible inhibition of the HER family receptors may improve PFS without improvement in OS in unselected

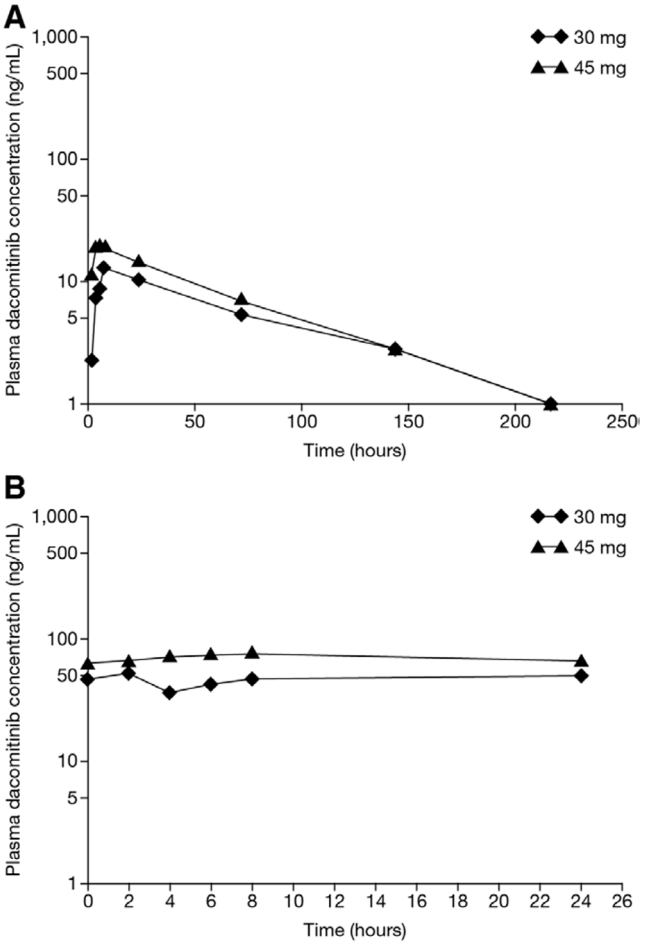


FIGURE 4. Median dacomitinib plasma concentration–time plots on cycle 0 day –9 (30 mg and 45 mg, single dose) (*A*); and on cycle 1, day 14 (30 mg and 45 mg, multiple dose), for dose-compliant patients (*B*).

patients with refractory NSCLC that have failed to respond to both EGFR TKIs and chemotherapy.

The impact on patients of treatment-related side effects and therapy-mediated modulation of disease symptoms are increasingly recognized as key elements of cancer care, particularly in late-stage, noncurative settings.[31] Patients in this clinical trial were less symptomatic at baseline than the EORTC reference population.[20] However, they still reported improvement in lung cancer symptoms of cough and pain in chest/arm/shoulder, beginning as early as the third week of therapy. These improvements appeared to be durable while patients remained on treatment. According to PRO, gastrointestinal class-effect toxicities peaked early in therapy (cycle 2, week 3), but were manageable and improved over time with intervention, despite minimal treatment guidelines for diarrhea, mucositis, and skin toxicity in this trial. This is the first study to report the impact of EGFR TKI-related skin toxicity exclusively in Korean patients. Although many patients reported skin toxicity symptoms at baseline, skin toxicity had a longer time to peak onset (cycle 5, week 12) than gastrointestinal toxicity. At its worst, skin toxicity was shown to have a "moderate effect" on patients' lives over the prior week. Ongoing phase III studies include a recommendation for proactive and early interventions to reduce the frequency and severity of dermatologic and gastrointestinal adverse events, and a toxicity prevention study is ongoing (NCT01465802).

Dacomitinib systemic exposure increased with increasing dose in this study, with PK parameters increasing dose-proportionally at the dose levels evaluated. The observed R_{ac} and dose-normalized parameters such as C_{max}, AUC_{inf}, and C_{trough} suggest that dacomitinib has linear kinetics after single- and multiple-dose administration of 30 mg and 45 mg doses. Furthermore, PK parameters observed in Korean patients after single- and multiple-dose administration of dacomitinib in this study seem similar to prior observations in studies with Western and Japanese patients.[6,21–23]

At the time the current study was designed, available data suggested a possible relationship between tumor response to gefitinib and serum levels of soluble EGFR, with no such relationship apparent for soluble HER2.[32] Subsequently, a retrospective analysis noted that pretreatment level of soluble EGFR more than 55 ng/ml was significantly associated with prolonged survival,[33] whereas high pretreatment level of soluble HER2 was a negative prognostic indicator.[34] More recently, tumor-specific soluble EGFR isoforms have been identified, raising the possibility that highly specific assays are required to evaluate potential biomarkers.[35] The exploratory analyses of the present study did not support a role for either soluble EGFR or soluble HER2 as biomarkers of dacomitinib efficacy, despite encouraging disease control. Further prospective studies are needed to evaluate potential biomarkers, particularly as diminishing levels of soluble HER2 in individual patients responding to dacomitinib are not unprecedented.[36]

CONCLUSION

In summary, dacomitinib demonstrated encouraging disease control and an acceptable safety profile in Korean patients with *KRAS* wild-type adenocarcinoma of the lung. However, it has been reported[37] that recently completed phase III studies of dacomitinib in unselected patients as second/third-line treatment and for refractory NSCLC failed to meet the primary end point (data currently unpublished). In this present study, patient selection was directed by clinical, histologic, and molecular parameters, resulting in a high likelihood of the presence of an *EGFR*-sensitizing mutation. The results reported here support robust biomarker collection to support evaluation of clinical trial outcomes in order to identify the subset of patients with refractory NSCLC who are most likely to benefit. A phase III trial is underway to determine the efficacy and safety of dacomitinib versus gefitinib in previously untreated patients with activating mutations in exon 19 or 21 (ARCHER 1050; NCT01774721).

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