CLINICAL INVESTIGATION

Rationale and study design of ARCHER: a randomized, double-blind, Phase III study of dacomitinib versus erlotinib for advanced non-small-cell lung cancer

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Background: Dacomitinib (PF-00299804) is an irreversible pan-HER tyrosine kinase inhibitor. We describe the rationale and design of a Phase III, randomized, double-blind study of dacomitinib versus erlotinib in patients with advanced non-small-cell lung cancer (NSCLC) following one or two prior lines of therapy in the advanced setting. **Method:** The primary end point of the study is progression-free survival per independent radiologic review in two co-primary patient populations: all patients with NSCLC (~800) and patients with confirmed KRAS wild-type NSCLC (at least 400). The study is powered to detect ≥33 and 45% improvement in progression-free survival in all NSCLC and KRAS wild-type NSCLC, respectively. The sample size will allow assessment of difference in overall survival in the co-primary populations with adequate power (i.e., ≥80%).

Keywords: dacomitinib • EGFR • erlotinib • human *EGFR* • *KRAS* • non-small-cell lung cancer • NSCLC • Phase III • targeted therapy

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Advanced non-small-cell lung cancer (NSCLC) continues to represent a major therapeutic challenge. Available standard platinum-based chemotherapeutic regimens for first-line treatment of patients with advanced NSCLC offer only modest survival benefits with a hazard ratio (HR) of 0.87 (p = 0.005) [1]. Following progression after first-line therapy, monotherapy with docetaxel or pemetrexed provides limited additional benefit in progression-free survival (PFS), overall survival (OS) or stabilization of NSCLC symptoms. Another widely used second-line treatment option is to target the EGF receptor (EGFR) using a reversible tyrosine kinase inhibitor (TKI). As cancer treatment moves from a paradigm of nonselective to individualized approaches, the further development of novel molecularly targeted agents has reached the center-stage for NSCLC.

The EGFR pathway has emerged as a leading therapeutic target for NSCLC based on its critical role in tumor proliferation, angiogenesis and evasion of apoptosis. The members of the HER/EGFR family of receptors include EGFR/HER-1, HER2/neu/erbB-2; HER3/erbB-3; and HER4/erbB-4. Signaling through these receptors, which is initiated by homo- and hetero-HER receptor dimerization, regulates tumor-cell proliferation, invasion, angiogenesis, metastasis and apoptosis for a number of human malignancies [2], including, prominently, NSCLC [3,4]. In addition, overexpression of these receptors is linked with more aggressive disease behavior and poorer disease outcome [5].

Gefitinib and erlotinib are selective and reversible EGFR/HER-1 TKI that are in use for the treatment of advanced NSCLC. Objective response rates of approximately 10–20% were observed in initial studies with gefitinib and erlotinib in patients with refractory NSCLC [6–8], and led to further Phase III studies. In the BR.21 randomized Phase III trial in advanced NSCLC, patients who received one or two prior chemotherapy regimens demonstrated PFS of 2.2 months and

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1.8 months (HR: 0.61; p < 0.001) and OS of 6.7 and 4.7 months (HR: 0.70; p < 0.001) for the erlotinib and placebo group, respectively [9]. The response rates were 8.9% in the erlotinib group and <1% in the placebo group (p < 0.001). Furthermore, erlotinib prolonged time to deterioration of cough, dyspnea, and pain versus placebo [10]. Based on the results of this study, erlotinib has been approved for use in unselected patients with NSCLC in the second- and third-line setting after failure of first-line platinum-based chemotherapy. More recently, erlotinib has been shown to be comparable to second-line chemotherapy in pretreated patients with NSCLC [11], as well as in a population of patients who progressed within four cycles of chemotherapy (TITAN trial) [12]. Interestingly, median OS was slightly longer with erlotinib than with chemotherapy for patients with *EGFR* wild-type (WT) tumors in this Phase III trial.

Mutations of *KRAS*, which encodes KRAS, a GTPase, participating in the intracellular transduction of the EGFR activation signal, are recognized as negative predictors of benefit from EGFR-targeted therapy in metastatic colorectal cancer. In the setting of advanced NSCLC, the issue of *KRAS* as predictive of outcome is less clear. In a meta-analysis of NSCLC studies, mutant *KRAS* emerged as a negative prognostic factor for OS [13], and *KRAS* mutations have been shown to be negative predictors of objective response to EGFR TKIs in advanced NSCLC (although this information has come from a relatively small number of samples available for molecular testing). However, in terms of other efficacy outcomes, a clear correlation between *KRAS* status and improvement in PFS and OS has not been consistently demonstrated in Phase III trials in various NSCLC settings [14].

Dacomitinib

Dacomitinib (PF-00299804) is a quinazoline-based orally available small molecule irreversible pan-HER TKI that covalently interacts with the unpaired cysteine residue within the ATP binding pocket of the tyrosine kinase. Dacomitinib potently inhibits all three catalytically active members of the HER family, with IC_{50} values of 6.0, 45.7 and 73.7 nmol/l for EGFR, HER2 and HER4, respectively.

As suggested by Wissner and Mansour, there are several potential advantages of an irreversible TKI compared with reversible competitive inhibitors such as erlotinib or gefitinib [15]. These include:

- Extended duration of tyrosine kinase blockade;
- A pharmacokinetic advantage in the presence of high intracellular ATP concentrations;
- Maintained target inactivation despite falling plasma concentrations of the inhibitor;
- Potential for better selectivity;
- Potential to treat tumors that are resistant to reversible TKIs [14].

Indeed, irreversible pan-HER TKIs have shown preclinical activity against both *EGFR* WT and mutant variants (sensitizing and resistance mutations) [16–18].

We conducted a global, multicenter, randomized Phase II study to compare dacomitinib with erlotinib in patients with advanced NSCLC to further evaluate the preclinical observations of irreversible EGFR blockade. The study enrolled 188 patients who had received one or two prior regimens of systemic therapy for advanced NSCLC [19]. Patients were required to have measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST), Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, and to provide tissue for molecular testing of *KRAS* and *HER* family receptors. No prior EGFR targeted therapy was allowed. Patients were randomized, with stratification for histology, smoking status and ethnicity, to receive either dacomitinib 45 mg once daily or erlotinib 150 mg once daily. The primary end point of the trial was PFS. Secondary end points included best overall response; duration of response (DR); OS; evaluation of the safety profile; patient-reported outcomes of health status, health-related quality of life, and disease-/treatment-related symptoms; determination of *KRAS* and *HER*-family mutations in tumor tissue; and pharmacokinetic analyses. *KRAS* and *EGFR* mutational status was determined in tumor tissue from 80 and 81% of patients, respectively. Patients were seen every 4 weeks for evaluation of safety (including laboratory) parameters. Tumor assessments per RECIST were performed at baseline and at weeks 8, 12, 16, 20, 24, and every 8 weeks thereafter.

Patient characteristics at baseline were well-balanced between treatment arms except for ECOG PS 2 (dacomitinib, n = 19; erlotinib, n = 3), *EGFR* mutation (dacomitinib, n = 19; erlotinib, n = 11), and a number of patients receiving two prior chemotherapy regimens (dacomitinib, n = 40; erlotinib, n = 27). In order to address the observed imbalances in key prognostic factors for benefit from HER-directed therapy in NSCLC (*EGFR* mutation, and baseline ECOG PS) stratified log-rank analyses were conducted. Dacomitinib demonstrated significantly longer PFS versus erlotinib in the overall population (2.86 vs 1.91 months; HR = 0.66; 95% CI: 0.47–0.91; 2-sided p-value = 0.012), with benefit consistent across several clinical and molecular subgroups (Figure 1) [19]. PFS in the *KRAS* WT subset population favored dacomitinib with a HR of 0.55

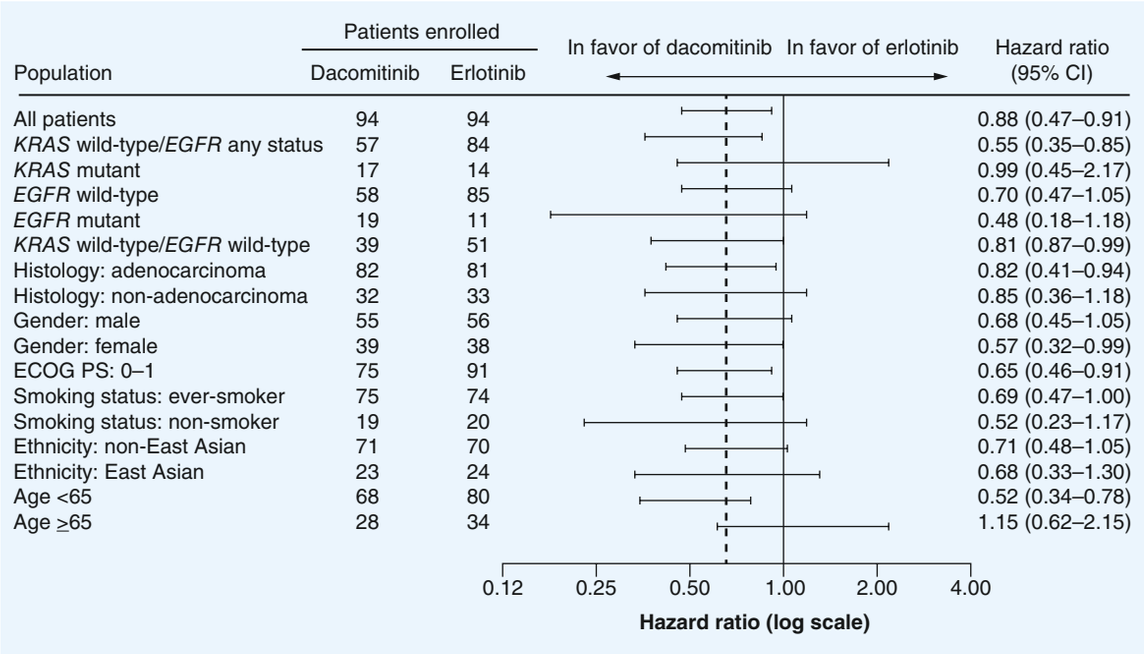

Figure 1. 1028 Subgroup analysis for progression-free survival.
ECOG PS: Eastern Cooperative Oncology Group performance status.

(95% CI: 0.35–0.85) and a 2-sided p-value of 0.006 versus erlotinib. The median PFS in this subgroup was 3.71 months for dacomitinib versus 1.91 months for erlotinib. A numerical trend towards improved OS with dacomitinib relative to erlotinib was observed that did not reach statistical significance. In addition, improvements were demonstrated in several key NSCLC symptoms for dacomitinib relative to erlotinib [20]. Clinical benefit response rate (complete response + partial response + stable disease ≥ 24 weeks) was favorable with dacomitinib compared with erlotinib. Common EGFR TKI treatment-related adverse events including skin events, diarrhea and stomatitis or mucositis were more frequent with dacomitinib than with erlotinib, but were manageable with standard supportive care. There was no evidence of cardiac toxicity due to HER2 targeting. Pharmacokinetics following 45 mg daily dosing were consistent with those previously reported [21], with no differences observed between ever-smokers and non-smokers, or according to the *EGFR* or *KRAS* mutational status of patients' tumors [Pfizer Inc. data on file].

Based on these encouraging Phase II results for dacomitinib compared with erlotinib, including benefit across multiple molecular and clinical subsets, a Phase III trial, the ARCHER (1009) study, has been initiated.

ARCHER (1009) study

This is a multinational, multicenter, randomized, double-blinded, double-dummy, Phase III clinical trial comparing the efficacy and safety of treatment with dacomitinib with treatment with erlotinib in patients with locally advanced or metastatic NSCLC who have previously had one (and no more than two) chemotherapy regimen. In order to fully investigate the benefit across key subsets, tissue for molecular analysis will be obtained from all patients, and efficacy will be analyzed within the following two co-primary populations:

- All enrolled patients with advanced NSCLC;
- Patients confirmed as having *KRAS* WT NSCLC (*KRAS* WT).

In this Phase III trial approximately 800 patients (≥400 *KRAS* WT) are to be randomized (1:1) to receive either dacomitinib or erlotinib. Administration is orally on a continuous daily basis. Patients are stratified at randomization by key prognostic factors for efficacy of EGFR TKIs administered in the second-line setting including histology (adenocarcinoma vs non-adenocarcinoma), race (Asian vs non-Asian and Indian subcontinent race), ECOG PS (0–1 vs 2) and smoking status (never-smoker, defined as ≤ 100 cigarettes, cigar or pipe lifetime vs ever-smoker). The primary analysis using stratified log rank test will include baseline ECOG PS status, *KRAS* status, and *EGFR* status as the stratification factors. A summary of the study design is presented in Figure 2.

Objectives

The primary objective of the trial is to investigate whether dacomitinib treatment is superior to erlotinib

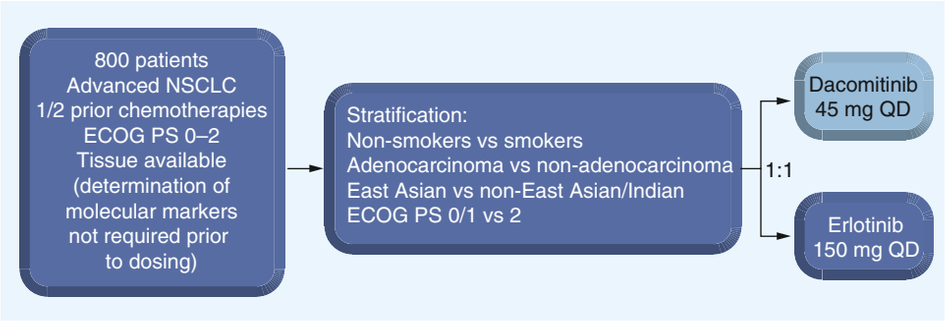

Figure 2. ARCHER study design.
ECOG PS: Eastern Cooperative Oncology Group performance status; NSCLC: Non-small-cell lung cancer; QD: Once per day.

treatment with respect to PFS per independent radiologic review in either of the co-primary populations: all patients and patients with *KRAS* WT tumors.

Secondary objectives include assessments of OS, PFS per investigator's assessment, objective response rate and DR; safety and tolerability; and patient-reported outcomes of health-related quality of life, and disease-/treatment-related symptoms between arms in the co-primary populations. *KRAS* and *HER*-family genotypes will be determined in tumor tissue samples. Plasma levels for dacomitinib and circulating metabolites will be assessed.

Key eligibility criteria

To be eligible for the study, patients should be aged ≥ 18 years, and have pathologically confirmed advanced NSCLC with ECOG 0–2 PS and radiologically measurable disease by RECIST. Patients must have received prior treatment with at least one and no more than two regimens of systemic therapy, including at least one standard chemotherapy for advanced NSCLC. Discontinuation of any systemic anticancer drug due to intolerance following administration of at least one full dose counts as one regimen. Similarly, substitution of one component of a combination drug regimen following administration of at least one full dose of the agent is considered the start of a new regimen (with the exception of substitution of the platin component of a cisplatin or carboplatin doublet). Prior investigational therapy in combination with a standard chemotherapy for NSCLC is also counted as one regimen of systemic therapy. Any prior treatment (chemotherapy, radiation, or surgery) must have been completed at least 2 weeks prior to randomization. A specimen from archival or recently obtained tumor tissue is required and will be sent to a central laboratory for molecular testing, including *KRAS* mutation status and *HER*-family testing (results of testing are not needed prior to randomization or initiation of therapy). Brain metastases treated with radiation or surgery are allowed if radiologically and neurologically stable and the subject discontinued corticosteroids at least 2 weeks prior to randomization. Adequate renal and liver function are required. Patients with known leptomeningeal metastases, or symptomatic brain metastases, patients who have received prior EGFR-targeted therapy, patients with uncontrolled or significant cardiovascular disease or with uncontrolled hypertension are not eligible.

Treatment plan

Upon meeting eligibility criteria including submission of tissue specimen to a central laboratory, patients will be randomized to receive either dacomitinib 45 mg and erlotinib placebo (Arm A) or erlotinib 150 mg and dacomitinib placebo (Arm B) taken orally once daily.

For the purpose of scheduling evaluations, a treatment cycle is designated as 28 days. Tumor assessment will be performed by CT or MRI scans at baseline (up to 28 days prior to start of treatment), at the end of cycles 2, 3, 4 and then every other cycle. Objective tumor response will be measured using RECIST version 1.1 and assessed by an independent review committee and by the investigator.

Left ventricular ejection fraction determination by echocardiogram or multigated nuclear imaging will be performed within 4 weeks prior to randomization, and repeated using the same technique at the end of cycles 3 and 6 and every six cycles thereafter. All patients will be followed up for subsequent cancer therapies and survival status regardless of the reasons for discontinuation from study drug treatment.

Anticipated results

This study will compare the benefit – including both PFS and OS, as well as objective response rate, DR, safety and patient reported outcomes – of once-daily oral administration of an irreversible pan-HER inhibitor with the selective reversible EGFR/HER1 TKI, erlotinib, in patients with advanced NSCLC after failure of initial chemotherapy. These results will be analyzed according to relevant clinical (e.g., histology) and molecular subsets (including *KRAS* and *EGFR*).

Statistical rationale for study design and interim analysis

A minimum of 617 PFS events are required to have 90% power to detect at least 33% improvement in PFS in all patients receiving dacomitinib versus erlotinib

(i.e., HR ≤ 0.75) using a one-sided, stratified log-rank test at a significance level of 0.015. A minimum of 313 PFS events are required to have 80% power to detect at least 45% improvement in PFS in *KRAS* WT patients receiving dacomitinib versus erlotinib (i.e., HR ≤ 0.69) using a one-sided, stratified log-rank test at a significance level of 0.01.

The study will be considered positive if the stratified log-rank test for PFS is significant, at the respective significant levels specified above, at the time of the final analysis for either of the two co-primary populations [22]. The stratified log-rank test in the final primary analysis will include baseline ECOG PS status, *KRAS* and *EGFR* mutation status as stratification factors, thus allowing a comparison between arms that accounts for the key predictive factors of benefit from EGFR TKI therapy. The sample sizes described above will also allow the assessment of difference in OS in the co-primary populations with adequate power and the same one-sided α split as for the analysis of PFS. It is anticipated that the follow up for survival will be approximately 7.4 months in all patients and 10.6 months in *KRAS* WT patients. The Type 1 error rate will be split between the co-primary populations to preserve the overall Type 1 error rate (α) for the study at 0.025, one-sided. It is estimated that at least 50% of enrolled patients will be determined to be *KRAS* WT; the study will enroll a total of approximately 800 patients with at least 400 patients confirmed as *KRAS* WT in approximately 20 months.

An interim analysis of PFS for futility will be conducted in the co-primary populations using PFS per investigator's assessment. The interim analysis will be conducted after approximately a third of PFS events (i.e., 104 events) for *KRAS* WT patients have occurred, at which time approximately 39% of PFS events (i.e., 245 events) are anticipated to have occurred for all patients. The interim analysis is expected to occur after approximately 9.5 months. The study will not be stopped for efficacy based on comparison of PFS at the interim analysis.

In order to place the ARCHER trial in a broader perspective it should be noted that whilst erlotinib and gefitinib are approved agents for the treatment of NSCLC, development of further reversible EGFR TKIs has been met with limited success [23]. However, available data for irreversible TKIs, of which dacomitinib and afatinib are the most advanced in clinical development, are promising. Afatinib is under evaluation in the LUX-lung clinical trial program [24], with Phase III trials versus chemotherapy in the first-line setting in patients with *EGFR* mutations [25], as well as in the second-line and refractory setting in unselected NSCLC patients with respect to *EGFR* mutation status. In addition to the ARCHER study, dacomitinb is under Phase III evaluation in an unselected patient population in the refractory setting in the BR26 trial following positive activity signals from a Phase II study [101]. Dacomitinib has also shown efficacy in the first-line setting in patients with *EGFR*-mutant tumors meriting further investigation in this setting in a planned Phase III trial [26].

Future perspective

Reversible EGFR TKIs have shown benefit for patients with advanced NSCLC following first-line systemic therapy. Irreversible TKIs affecting several receptors of the related/complementary pathways may potentially offer additional benefit and even overcome some of the mechanisms of resistance to reversible, single receptor-targeted TKIs. Ongoing studies using single or combinations of targeted agents should, in the coming years, provide improved therapeutic options for most patients with NSCLC, while implementing our understanding of tumor-driving intracellular pathways, specific biomarker-defined subgroups and resistance mechanisms to available agents.

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Executive summary

Dacomitinib

- Dacomitinib (PF-00299804) is an irreversible pan-HER tyrosine kinase inhibitor that has shown encouraging activity against advanced non-small-cell lung cancer when compared with erlotinib in a Phase II study.

ARCHER (1009) study

- A randomized, double-blinded Phase III clinical trial, ARCHER 1009, is designed to compare the efficacy and safety of treatment with dacomitinib to treatment with erlotinib in patients with locally advanced or metastatic non-small-cell lung cancer following one (and no more than two) prior chemotherapy regimens.

Objectives

- In addition to evaluation of progression-free survival (PFS) per independent review in co-primary populations (all patients and patients with *KRAS* wild-type tumors) as the primary objective, the ARCHER 1009 trial will assess overall survival, PFS per investigator's assessment, objective response rate, duration of response, safety/tolerability, and patient reported outcomes.
- The study will enroll a total of approximately 800 patients, with at least 400 confirmed as *KRAS* wild-type.
- Patients are randomized (1:1) to receive either dacomitinib 45 mg or erlotinib 150 mg once daily.

Statistical rationale for study design & interim analysis

- The ARCHER 1009 trial is designed to have 90% power to detect at least 33% improvement in PFS in all patients receiving dacomitinib versus erlotinib at a significance level of 0.015 using a one-sided, stratified log-rank test.
- The ARCHER 1009 trial is also designed to have 80% power to detect at least 45% improvement in PFS in patients with *KRAS* wild-type disease receiving dacomitinib versus erlotinib at a significance level of 0.01 using a one-sided, stratified log-rank test.

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■■ **Report on dacomitinib 1017 Phase II trial in patients with advanced NSCLC for first-line treatment of *EGFR*- or *HER2*-mutant or -amplified tumors. Study investigators reported that in the *EGFR*-mutant cohort with *EGFR* exon 19 or 21 mutant lung cancers, 95.5% (95% CI: 83.2–98.9) of patients (n = 45) were progression free at 4 months, the primary end point of the study, while the preliminary median PFS for these patients was 18.2 months (95% CI: 12.8–23.8). Of note, 76.4% (95% CI: 60.6–86.6) of these patients remained progression free at 1 year. Additionally, 76% of patients in this cohort experienced a partial response (95% CI: 59–86). In 22 patients with HER2 lung cancer, three partial responders and six stable disease were noted as best objective response to date.**

■ Website

101 ClinicalTrial Database: NCT01000025. www.clinicaltrials.gov/show/NCT01000025